March Research on Non-Newtonian fluids

Done: Started to read book *Cardiovascular mathematics* and different papers e.g. *Methods of Blood Flow Modelling* (see Notion-Files
`https://www.notion.so/22348433906041bc96a58526e35ab922?v=ce689bf670d9451c9c8a0eb71093342d`
for full list of literature)

Subjects

1. Familiarization with the properties and modeling of blood flow
2. Rheological models for blood - Research on modelling approaches for Non-Newtonian Fluids - In particular which model is suited for blood flow
3. Derivation of Navier-Stokes Equation - How is the assumption for Newtonian fluids integrated (linked with subject 2)

1 Familiarization with the properties and modeling of blood flow

1.1 Book Cardiovascular mathematics

Properties of blood and cardiovascular system in general

"Blood is in fact a suspension of cells and particles in plasma. A Newtonian constitutive equation is generally accepted as a good approximation of blood behaviour for large vessels. However, the study of circulation in smaller vessels and capillaries needs to abandon the Newtonian assumption for the fluid and account for the shear-thinning behaviour of blood."(Preface)

"The more it [blood] stirs the more it fluidifies (just think to the behaviour of tomato ketchup, another shear-thinning fluid). In other words, its (apparent) viscosity decreases with the increase of the rate of deformation. This effect is stronger in smaller vessels, like the arterioles, venules and the capillaries. Viscoelastic effects can be very important at the fine spatial scale (micro-circulation)[...]."(Chapter 2)

Shear-thinning behaviour: In rheology, shear thinning is the non-Newtonian behavior of fluids whose viscosity decreases under shear strain. It is sometimes considered synonymous for pseudoplastic behaviour.

"The microcirculation is made up of three parts; the arterioles, the capillaries and the venules. These vessels are very small (5-30 μm in diameter) but very numerous so that local velocities are very small ($\approx$ 1mm/s). This means that the characteristic values of Re are very small so that viscous forces completely dominate any inertial forces in the flow. ***As a result, virtually all of the resistance to flow is found in the microcirculation****. This is not to say that viscous effects are not important in the large vessels, the no-slip condition at the vessel walls ensures that viscosity is important in determining the detailed distribution of flow in the large vessels. However, it does mean* ***that almost all of the pressure head losses in the circulation occur in the microcirculation****. Most of the pressure head losses actually occur in the arterioles. The arterioles have very thick muscular and highly ennervated walls; the ratio of wall tissues to lumen diameter is $\approx$1. The distribution of blood flow to different tissues is determined*

largely by these vessels whose resistance is highly dependent upon their diameter, which is controlled by contraction or relaxation of the smooth muscle in the wall."(Chapter 1)

"The capillaries are the smallest vessels in the circulatory system and they are responsible for the bulk of exchange between the blood and the various tissues. Capillaries range from 5-8μm in diameter and 200-400μm in length. The bore of most capillaries is smaller than the largest dimension of the red blood cells, which means that the cells pass through the capillaries in single file and they must deform during their passage. ***In the capillaries, therefore, blood can no longer be thought of as a homogeneous fluid and it is necessary to treat it as a multi-phase fluid composed of plasma and cells (particle flow).*** *"*(Chapter 1)

"There is a reduction in the effective viscosity of blood in the microcirculation (the Fahraeus-Lindquist effect) due to the steric exclusion of the blood cells from the wall regions of the vessels (the Fahraeus effect)."(Chapter 1)

Fahraeus-Lindquist effect: Short explanation video; Also interesting video (Video turbulence)
is an effect where the viscosity of a fluid, in this case blood, changes with the diameter of the tube it travels through; in particular there's a decrease of viscosity as the tube's diameter decreases. This is because erythrocytes (red blood cells) move over the center of the vessel, leaving plasma at the wall of the vessel. *("Below a critical vessel calibre (about 1mm), blood viscosity becomes dependent on the vessel radius and decreases very sharply. This is known as Fahraeus-Lindquist-effect. [..] red blood cells move to the central part of the capillary, whereas the plasma stays in contact with the vessel wall. This layer of plasma facilitates the movement of the red cells, thus causing a decrease of the apparent viscosity.")*(Chapter 2)

Fahraeus effect: is the decrease in average concentration of red blood cells in human blood as the diameter of the glass tube in which it is flowing decreases. In other words, in blood vessels with diameters less than 500 micrometers, the hematocrit decreases with decreasing capillary diameter. The Fahraeus effect definitely influences the Fahraeus-Lindquist effect, which describes the dependence of apparent viscosity of blood on the capillary size, but the former is not the only cause of the latter.
Reason: The Fahraeus effect occurs because the average RBC (red blood cell) velocity is higher than the average plasma velocity.

Mathematical Models

"The mathematical equations of fluid dynamics are the key components of haemodynamics modelling. Rigorously speaking blood is not a fluid but a suspension of particles in the plasma, the latter being mainly made of water. Most important blood particles are red cells (erythrocytes), white cells (leukocytes), and platelets (thrombocytes). Being the most numerous, red cells are the main responsible for the special mechanical properties of blood. The prominent macroscopic effect of their presence is that blood is a shear-thinning, or thixotropic fluid."(Chapter 2)

"Therefore, a first separation line between models for blood flow may be drawn: ***on one side the Newtonian model which neglects shear thinning and viscoelastic effects and is suitable in larger vessels*** *or when we are not interested in the finer details of the flow, as non-Newtonian behaviour may affect, for instance, the size of the recirculation area behind a severe stenosis. On the other side,* ***in vessels of diameter, say, less than 1mm the use of Newtonian models is hardly justifiable. The small velocities and shear stress here involved call for the use of one of the non-Newtonian models*** *described in Chapter 6. Computationwise, non-Newtonian models which just modify the expression for the viscosity by making it dependent on the shear rate would increase the cost of computations of*

approximately 10 percent, because of the extra calculations and the increased non-linearity of the problem. Full visco-elastic models may instead be much more costly in terms of computing time."(Chapter 2)

Model flow in large and medium sized vessels *"Flow is here governed by the Navier-Stokes equations*

$$\frac{\partial \boldsymbol{u}}{\partial t} + \rho(\boldsymbol{u} \cdot \boldsymbol{\nabla})\boldsymbol{u} + \boldsymbol{\nabla} P - \boldsymbol{div}(\mu \boldsymbol{D}(\boldsymbol{u})) = \boldsymbol{f} \tag{1}$$

$$\boldsymbol{div}(\boldsymbol{u}) = 0 \tag{2}$$

*"in a domain $\Omega \in R^3$ representing the lumen of the vessel, or system of vessels, under investigation. For a **Newtonian** fluid assumption the viscosity μ is kept constant.*

"The principal unknowns are the velocity $\boldsymbol{u}$ and the pressure P, while the density ρ is here constant. The term $\boldsymbol{f}$ in the right hand side accounts for the possible action of external forces, like gravity, and is often taken equal to zero in haemodynamics."(Chapter 2)

Boundary conditions and Initial conditions

"The equations have to be supplemented with boundary conditions on $\partial\Omega$. We typically prescribe a velocity profile at the proximal boundary Γ in, that is the section closest to the heart along the direction of the mean blood flow, which we will also denote as inflow boundary, even if the term inflow in not completely correct since in some major vessels we can have flow reversals. We then prescribe zero velocity at the fixed walls and the normal stresses $\boldsymbol{T} \cdot \boldsymbol{n}$ at the distal boundaries Γ_{out} (also called outflow boundaries). Again, the term distal is meant with respect to the heart.

*We need also to prescribe the initial status of the fluid velocity, for instance $\boldsymbol{u}(\boldsymbol{x}, 0) = \boldsymbol{u}_0(\boldsymbol{x})\boldsymbol{x} \in \Omega$, being $\boldsymbol{u}_0$ a given quantity. We recall that $\boldsymbol{u}_0$ cannot be arbitrary, since it has to satisfy $\boldsymbol{div}\boldsymbol{u}_0 = 0$ to be admissible ! Unfortunately, in haemodynamics computations usually we do not know a physically relevant initial condition. Therefore $\boldsymbol{u}_0$ is usually chosen rather arbitrarily, often just equal to zero everywhere. It means that numerical computations may suffer a false transient linked to the incorrect initial data. If the boundary conditions are correct, however, it will decay quite rapidly.(...) A possibility to get a better guess of the initial data is to **solve a stationary Stokes problem**"*(Chapter 2)

"The situation is worsened when the compliance of the wall is taken into account. The continuous exchange of energy between fluid and wall effectively makes the decay slower. In calculations of flow in compliant vessels it is normal practise to wait for at least three cardiac cycles before considering the influence of the initial data negligible"(Chapter 2)

Properties of equations

*"The solution of the Navier-Stokes equations may develop instabilities, which are normally called turbulence. The responsible is the dynamics induced sure the importance of this term compared with the diffusive part given by by the non-linear convection term $\rho(\boldsymbol{u} \cdot \boldsymbol{\nabla})\boldsymbol{u}$. It is therefore natural to measure the importance of this term compared with the diffusive part given by $\boldsymbol{div}(\mu \boldsymbol{D}(\boldsymbol{u}))$. This information is provided by the Reynolds number. **If the Reynolds number is small, say at most of the order of 1000, the flow remains stable, and is called laminar**. In normal physiological situations, then,*

the values of the Reynolds number reached in the cardiovascular system do not allow the formation of full scale turbulence. Some flow instabilities may occur only at the exit of the aortic valve and limited to the systolic phase. In this region the Reynolds number may reach the value of few thousands only for the portion of the cardiac cycle corresponding to the peak systolic velocity, however, there is not enough time for a full turbulent flow to develop. ***When departing from physiological conditions, there are several factors that may induce transition from laminar to turbulent flows. For instance, the increase of flow velocity because of physical exercise, or due to the presence of a stenotic artery or a prosthetic implant such as a shunt, may produce an increase of the Reynolds number and lead to localised turbulence. Smaller values of blood viscosity also raise the Reynolds number****; "*(Chapter 2)

"Knowing the velocity and the pressure fields allows the computation of the stresses, in particular the shear stresses to which an arterial wall is subjected due to the blood movement. Wall shear stresses, are the force per unit area exerted by the fluid tangentially to the wall. We have already mentioned their importance in relation with some vascular diseases, since endothelium cells react to shear stresses.Irregular, and in particular small or ***oscillating shear stresses*** *[Wall shear stress is considered to be oscillating when its component along the main flow direction changes sign during the heart beat. In normal situations the component of wall shear stress along the main flow is always negative. Oscillating shear stresses are usually found in recirculation regions.] may cause an alteration in the endothelium covering and induce inflammatory processes. Their calculation require a point-wise knowledge of the velocity and pressure field! To account for the compliance of the vessel wall we need to introduce another unknown, namely the wall displacement* $\boldsymbol{\eta}$*"*(Chapter 2)

FSI

Smaller vessels experience a smaller relative movement than larger ones, where the change of radius during the heart beat may be of the order of 15 percent , like in the aorta. Therefore, the flow in the peripheral vessels, lets say more than two branching levels down from the aorta, can be reasonably modelled using a fixed geometry. ***An exception*** *being the coronaries, whose movement is however dominated by the heart movement more than the fluid-structure interaction in the vessel. The effect of heart movement in the shear stress distribution in a coronary artery has been investigated. It has been found that it can be relevant, particularly in vessels with high curvature. Even in the larger vessels, at least in physiological situations, the main characteristic of the flow are already captured by a fixed geometry model.* ***However, if more details are needed, such as a precise computation of shear stresses or the size of a recirculation region, then compliant models are better suited. Furthermore, if it is necessary to have an accurate description of pulse waves, for instance if one wants to investigate altered pressure pattern possibly caused by anomalous pulse wave reflections, like in the study of aortic aneurysms [285], then compliant models are mandatory****. The reason is that fixed geometry models simply cannot describe pulse waves: the propagation speed is here infinite because of the incompressible fluid. It is indeed the mechanical interaction between blood flow and vessel wall deformation that generates the pulse waves."*(Chapter 2)

General

A clear major feature of blood flow is its pulsatility. It may induce flow reversal and recirculations near the arterial wall, a phenomenon that can have negative effects on the endothelium and stimulate the deposit

of lipids and atherosclerosis. The latter effect is more likely to occur in specific vascular districts, like the carotid bifurcation"(Chapter 2)

With some approximation one may think that blood flow is periodic in time. Yet, this can be considered true only for relatively short periods, since the various human activities require to change the amount of blood sent to the various organs. Also the elastic properties of arteries (especially the arterioles) may vary depending on the request of blood by the peripheral organs. Indeed one of the aspects of current research in computational haemodynamics is the interaction between blood flow and the metabolic regulation. It presents several challenges from the mathematical modelling and numerical side. For the sake of space and because only partial results are available so far this aspect has not been extensively covered in this book (see Chapter 10). In several early studies, however, blood computations were made ***using steady flow. This can be considered acceptable in peripheral arteries, the capillary bed and in the veins,where the pulsatility of the flow is reduced thanks to the regularising effect of the compliance of the major arteries. In particular, micro-circulation is practically (but not completely) steady. The use of steady computations in larger vessels may again by justified by the lower computational cost.***(Chapter 2)

(Temperature)

We mention that in some particular contexts, for instance in the hyperthermia treatment where some drugs are activated through an artificial localised increase in temperature (see [123, 219]), the variation of blood temperature may be relevant. Describing the evolution of temperature requires to introduce another partial differential equation which derives from the principle of energy conservation, and couple it with the Navier-Stokes equations. In large and medium sized vessel the coupling is weak, since here temperature variations have small influence in the flow field.[...] ***Things are different in micro-circulation, where the combined effect of temperature on the blood apparent viscosity and on other mechanical properties of the vessel wall makes the situation more complex [178]. However, since in the physiological regime the temperature inside the human body is constant and the situations where temperature variations are relevant are rather special, we will not pursue this topic further in this book)***(Chapter 2)

Mathematical Derivation

ALE *As already mentioned in Chapter 2, in many cases of practical interest in haemodynamics, such as blood flowing in a compliant artery, the computa- tional domain for the fluid cannot be fixed in time, as it has to follow the displacements of the fluid-wall. Yet, the Lagrangian frame is not of help here, since certainly we do not wish to follow the evolution of the blood particles as they circulate along the whole cardiovascular system! We usually wish to compute the flow field in a domain confined in the area of interest, yet following the movement of the wall interface. The computational domain, which we will now indicate with $\omega(t)$, is neither fixed nor a material subdomain, since its evolution is not governed by the fluid motion, but has to comply by that of the boundary $\partial\omega(t)$, which is either given or the result of the coupling with a structural model. It is then necessary to introduce another, intermediate, frame of reference, called Arbitrary Lagrangian Eulerian (ALE).*

Navier-Stokes Equations and Boundary conditions

see Derivation of NS-Eqs

Chapter 4 is image processing

Chapter 5 key flow paramaters

Reynolds number,Re_D, is overall the pre-eminent parameter, both in determining the stability of a flow and the persistence of geometric influences downstream of a bend or other disturbance. The reduced velocity, U_{red} is a more appropriate parameter than the Womersley number for unsteady flows where there are significant streamwise flow variations. The Dean number De is the dominant parameter used to characterise flow in bends; in tightly curved or helical bends other parameters in addition to De may be required.

Chapter 6 is rheology of blood - see section 2

1.2 Paper A heterogeneous multi-scale model for blood flow

Motivation for multiscale modeling

"Blood flow on scales larger than 300μm is consistently modeled as a continuous fluid, as it is computationally more convenient because models no longer include the individual cell dynamics which greatly reduces the computational overhead. Continuous models either assume whole blood as a Newtonian fluid on larger scales or use a non-Newtonian blood viscosity model to approximate the departure of whole from the Newtonian description. Non-Newtonian models describe the change in blood viscosity with a dependency either on shear rate like a power law fluid [22] or Carreau-Yasuda [2], or depends on yield stress like the Casson model [19]. ***Since such models do not include the dynamics of the cells they may over estimate the transport behaviors which are a result of cell-cell collisions within whole blood suspensions****. This may lead to an invalid description of particle diffusivities within whole blood."*

"In order to capture both the non-Newtonian viscosity change of whole blood along with the proper treatment of the transport of suspended blood cells a multi-scale model must be developed in order to correctly account for both processes on all scales of the cardiovascular system. (...) A benefit of such an HMM model applied to blood flow is that on the largest scales a continuous blood flow solver will be informed by a micro scale cell resolved blood flow solver, resolving the cell nature of whole blood by keeping computational overhead in mind."

Very good schematic images about the method ....

2 Rheological models for blood

2.1 Cardiovascular mathematics (Chapter 6)

Rheology is the science of the deformation and flow of materials. It deals with the theoretical concepts of kinematics, conservation laws and constitutive relations, describing the interrelation between force, deformation and flow [...] The object of haemorheology is the application of rheology to the study of flow properties of blood and its formed elements [...]
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

Physical mechanisms behind the mechanical properties of blood

Whole blood is a concentrated suspension of formed cellular elements that includes red blood cells (RBCs) or erythrocytes (40-45 percent), white blood cells (WBCs) or leukocytes (around 1 percent) and platelets or thrombocytes (55-60 percent).

While plasma is nearly Newtonian in behaviour, whole blood exhibits marked non-Newtonian characteristics, particularly at low shear rates. The non-Newtonian behaviour of blood is mainly explained by three phenomena:

1. *the erythrocytes tendency to form a three-dimensional microstructure at low shear rates*
2. *their deformability*
3. *their tendency to align with the flow field at high shear rates*

The formation and breakup of this 3D microstructure, as well as the elongation and recovery of red blood cells, contribute to bloods shear thinning, viscoelastic and thixotropic behaviour (here we refer to thixotropy as the dependence of the material properties on the time over which shear has been applied. This dependence is largely due to the finite time required for the three-dimensional structure of blood to form and break down.)

Low shear rate behaviour: aggregation and disaggregation of erythrocytes

In the presence of fibrinogen and globulins (two plasma proteins), erythrocytes have the ability to form a primary aggregate structure of rod shaped stacks of individual cells called rouleaux. ***At very low shear rates the rouleaux align themselves in an end-to-side and side-to-side fashion and form a secondary structure*** *consisting of branched three-dimensional aggregates [...] For blood at rest, the three-dimensional structure formed by the RBCs appears* ***solid-like, appearing to resist flow until a finite level of force is applied*** *[...]*
When blood begins to flow, the solid-like structure breaks into three-dimensional networks of various sizes which appear to move as individual units and reach an equilibrium size for a fixed shear rate. Increases in shear rate lead to a reduction in equilibrium size and lower effective viscosity[...]

The process of disaggregation under increasing shear is reversible *When the shear rate is quasi-statically stepped down to lower values, the individual cells form shorter chains, then longer rouleaux and eventually a 3-D microstructure*

The finite time necessary for equilibrium of the structure to be reached (both during aggregation and disaggregation) is responsible for the thixotropic behaviour of blood at low shear rates
The associated time constants are a function of shear rate. The equilibria are found to be reached more rapidly at higher shear rates and more gradually with lower shear rates

High shear rate behaviour of whole blood: shear flow of dispersed erythrocytes

When blood is subjected to a constant shear rate ... the cells can be seen to rotate. With increasing shear rate, they rotate less and for shear rates above a value, they cease to rotate and remain aligned with the flow direction [...] (they) lose their biconcave shape, become fully elongated and are transformed into flat outstretched ellipsoids with major axes parallel to the flow direction. At this stage the collision of red cells only occurs when a more rapidly moving cell touches a slower one but there are no further interactions between the cells.

The high deformability of erythrocytes is due to the absence of a nucleus, to the elastic and viscous properties of its membrane and also to geometric factors such as the shape, volume and membrane surface area

Material blood

Many of the continuum models for blood are examples of a large category of ***constitutive models called incompressible simple fluids****. As defined in [100], ... an incompressible simple material . . . is a substance whose mass density never changes and for which the stress is determined, to within a pressure, by the history of strain. . . . We then define an incompressible simple fluid as an incompressible simple material with the property that all of its local configurations are intrinsically equivalent in response, with all observable differences in response being due to definite differences in history*

The mechanical response of incompressible Newtonian fluids in shear is completely determined by one material constant: the viscosity μ. The response of general fluids is much more complicated and can include behaviours not displayed by Newtonian fluids such as rod climbing, shear thinning and memory. Remarkably, the behaviour of an arbitrary simple fluid in a broad class of flows called ***viscometric flows*** *only requires knowledge of three material func- tions for that fluid. Appropriately, these three functions are called viscometric material functions and are intrinsic properties of the fluid*

Viscometric flow: *[...] that these are a special type of constant stretch history flow which, from the point of view of the fluid element, are indistinguishable from a steady simple shear flow described in terms of suitably chosen local Cartesian coordinates [...] three viscometric material functions are easily defined relative to simple shear flow*

1. *Viscosity or Shear Viscosity*
2. *First normal stress coefficient*

3. Second normal stress coefficient

Thixotropic response

The formation of the three-dimensional microstructure and the alignment of the RBC are not instantaneous, which gives blood its thixotropic behaviour. [..] Outside of industrial applications, these definitions largely focus on the time dependence of rheological properties under fixed shear rate (e.g. viscosity, normal stress effects) arising from the finite time required for the breakdown and buildup in microstructure such as that just described for blood

Constitutive models

We will assume that all macroscopic length and time scales are sufficiently large compared to time and length scales at the level of the individual erythrocyte that the continuum hypothesis holds. ***Thus the models presented in the pages that follow would not be appropriate in the capillary network****, for example, and for an overview of haemorheology in the microcirculation we refer the reader to the review articles of Popel and Johnson [393] and Pries and Secomb [394].[..]*
it is important to consider in which flow regimes and clinical situations the non-Newtonian properties of blood will be important: (page 231)

Possible locations where the non-Newtonian behaviour will be significant include segments of the venous system and stable vortices downstream of some stenoses and in the sacs of some aneurysms*.*

As a first step towards the macroscopic modelling of blood flow we recall the equations for the balance of linear momentum and conservation of mass (or incompressibility condition) for isothermal flow

$$\frac{D\boldsymbol{u}}{Dt} = -\boldsymbol{\nabla} P + \boldsymbol{div}(\boldsymbol{\tau}) \tag{3}$$

$$\boldsymbol{div}(\boldsymbol{u}) = 0 \tag{4}$$

Here, $\boldsymbol{\tau}$ denotes the extra-stress tensor accounting for differences in behaviour from a purely inviscid, incompressible fluid. To close the system of equations, we require an equation relating the state of stress to the kinematic variables such as rate of deformation of fluid elements. These constitutive equations and the elaboration of macroscopic constitutive models suitable for blood flow under certain flow conditions are the primary subjects of this section.

Newtonian

The simplest viscous fluid model is that due to Newton. On the assumption that the components of the extra-stress tensor are each linear isotropic functions of the components of the velocity gradient $\boldsymbol{\nabla u}$, it may be shown that for an incompressible fluid

$$\boldsymbol{\tau} = 2\mu \boldsymbol{D}(\boldsymbol{u})) \tag{5}$$

this leads to the well-known Navier-Stokes equations for an incompressible viscous fluid. ***This set of equations is commonly used with some justification to describe blood flow in the heart and***

healthy arteries *Blood is nonetheless non-Newtonian and in the previous sections evidence has been presented to show that under certain experimental or physiological conditions is inadequate as a constitutive relation for blood.*

we first Discuss representative rheologically admissible constitutive equations with shear thinning viscosity, and then introduce the ***Casson model****, a representative yield stress fluid*

Reiner-Rivlin-Fluids

Without loss of generality (e.g. [15]), the most general incompressible constitutive model of the form $\boldsymbol{\tau} = \boldsymbol{\tau}(\boldsymbol{\nabla u})$ *that respects invariance requirements*

$$\boldsymbol{\tau} = \phi_1(I_2, I_3)D(u) + \phi_2(I_2, I_3)D(u)^2 \tag{6}$$

where I_2 *and* I_3 *are the second and third principal invariants of the rate of deformation tensor,*

$$I_2 = \frac{1}{2}((tr(D(u))^2 - tr(D(u)^2)), \;\; I_3 = det(D(u)) \tag{7}$$

and trace is identically zero for divergence free velocity fields essential for incompressible fluids (isochoric motions). Incompressible fluids of the form (6.16) are typically called Reiner-Rivlin fluids. The behaviour of Reiner-Rivlin fluids with non-zero values of ϕ_2 *in simple shear does not match experimental results on real fluids [15]. In addition, the dependence on the value of* I_3 *is often considered negligible [15].*

Generalized Newtonian Fluids

General form

$$\tau = 2\mu(I_2)D(u) \tag{8}$$

where μ is the same viscosity (a viscometric function) defined in (6.1). In viscometric flows, I_3 is identically zero and it is not necessary to explicitly assume the dependence of μ on I_3 is negligible. The quantity I_2 is not a positive quantity, so it is useful to introduce a metric of the rate of deformation, denoted by $\dot{\gamma}$

$$\dot{\gamma} = \sqrt{2tr(D(u)^2)} = \sqrt{-4I_2} \tag{9}$$

the **generalised Newtonian model** takes then useful form,

$$\tau = 2\mu(\dot{\gamma})D(u) \tag{10}$$

Power law model

A simple example of a generalised Newtonian fluid is that of the power-law fluid, which has viscosity function given by

$$\mu = k\dot{\gamma}^{n-1} \tag{11}$$

k being a positive constant and n a constant chosen to have a maximum value 1, leading to a monotonic decreasing function of shear rate (shear thinning fluid) when $n < 1$ *and a constant viscosity (Newtonian) fluid when* $n = 1$*.* ***One of the major advantages of this model is that it is possible to obtain numerous analytical solutions to the governing equations. Two major drawbacks of the***

power-law model for the shear thinning case are that the zero shear rate behaviours are unphysical and limit the range of shear rates over which the viscosity is unbounded and the asymptotic limit as $\dot{\gamma} \longrightarrow \infty$ is zero. *Both these behaviours are unphysical and limit the range of shear rates over which the power-law model is reasonable for blood*

Extension of the power-law model from Walburn and Schneck

One of the more successful viscosity laws for blood is an extension of the power-law model due to Walburn and Schneck [534]. In addition to the shear rate, ***they considered the dependence of the viscosity on the haematocrit (H_t) and total protein minus albumin (TPMA) content through the parameter k and n in (6.21). Using a nonlinear regression analysis they found that shear rate and haematocrit were the two most important factors in decreasing order of importance.*** *Based on these two factors, they formulated the following expressions for k and n,*

$$k = C_1 exp(C_2 H_t), \qquad n = 1 - C_3 H_t. \tag{12}$$

They found an R-squared statistical increase from 62 percent to 88 percent when Ht was included in the power-law model in addition to shear rate. The statistical significance rose to nearly 91percent when TPMA was also added. Walburn and Schneck attribute the two parameter model (6.21) to Sacks [441].

Quemada model

In 1978 Quemada [412] used a semi-phenomenological approach to develop a constitutive law suitable for concentrated disperse systems (such as blood) that had an apparent viscosity μ determined from

$$\mu = \mu_f (1 - \frac{1}{2} \frac{k_0 + k_\infty \sqrt{\dot{\gamma}/\dot{\gamma_C}}}{1 + \sqrt{\dot{\gamma}/\dot{\gamma_C}}} \phi)^{-2} \tag{13}$$

where μ_F, ϕ and$\dot{\gamma_C}$ are the viscosity of the suspending fluid, the volume concentration of the dispersed phase and a critical shear rate.

Cassons equation

$$\sqrt{|\tau_{12}|} = \sqrt{K}\sqrt{\dot{\gamma}} + \sqrt{|\gamma_0|} \tag{14}$$

for the absolute value of the shear stress $|\tau_{12}|$ as a function of the shear rate when the magnitude of the shear stress exceeds that of a yield stress γ_0

The controversy over the existence of a yield stress and the use of it as a material parameter were introduced in Section 6.3.4. Here, we briefly sum- marise some of the results obtained for these measurements, but caution that measurements of the yield stress are expected to be quite sensitive to the microstructure of the blood prior to yielding, which is in turn expected to be sensitive to both the shear rate history as well as time [338] (...) and confirmed the importance of the presence of fibrinogen for the magnitude of the yield stress. Also haematocrit levels had to exceed a criti- cal threshold (typically between 0.05 and 0.08) for there to be a measurable yield stress. Results in the literature for the yield stress of blood show it to be very small, however:(..)

Material parameters for blood in generalised Newtonian andCassonmodels

see book *As discussed earlier in this chapter, the material parameters of blood are quite sensitive to the state of blood constituents as well as temperature. The dependence on temperature has been found to be similar to water*

Table 6.2 summarises some of the most common generalised Newtonian models that have been considered in the literature for the shear dependent viscosity of whole human blood.

As discussed earlier in this chapter, the material parameters of blood are quite sensitive to the state of blood constituents as well as temperature. The dependence on temperature has been found to be similar to water

Viscoelastic and thixotropic models

Experimental in vitro evidence for the viscoelastic behaviour of human blood and discussion of its connection with the storage and dissipation of energy during the distortion of the 3D microstrucure formed by the RBC at low shear rates abounds in the literature:

A word of caution is in order at this point, however. A study of blood in sinusoidal flows in glass tubes by Federspiel and Cokelet in 1984 [143] using tube diameters, flow rate amplitudes and oscillation frequencies that attempted to mimic those in small arteries indicated that blood elasticity was effectively negligible in this flow regime. Differences with measurements made earlier by Thurston [503] were attributed to the larger shear rates in Federspiel and Cokelets work, and Thurstons work was suggested as being more applicable to venous flow or pathological low-flow rate flows than arterial flow

In addition to being a viscoelastic fluid, ***the fact that red cell aggregates neither form nor break up instantaneously leads to blood being thixotropic*** *(see, Section 6.3.3) and the reader is also referred to [215,231,505], for example, for further discussion*

None of the above models iaccounts for either the viscoelasticity or the thixotropy of blood

Viscoelastic constitutive models of differential type, suitable for describing blood, have been proposed recently by Yeleswarapu [548, 549] and by Anand and Rajagopal [10] (the latter being developed in the context of the general thermodynamic frame- work of Rajagopal and Srinivasa [417])

The common outcome of the modelling done by all these authors is a ***generalised Maxwell-type equation for the stress due to the size and position distributions of the rouleaux****. Both viscosity and relaxation time are functions of a structure variable which, in the papers cited above, is either the number fraction of red blood cells in aggregates (more generally, aggregated particles) or of aggregated cell faces [5*

In 2006 Owens [141, 367] followed ideas drawn from the classical theory of network models for viscoelastic fluids to derive a relatively simple single-mode structure-dependent generalised Maxwell model for the contribution $\boldsymbol{\tau}$ of the erythrocytes to the total Cauchy stress. In the model developed in [141, 367] the erythrocytes were represented in their capacity to be transported, stretched and orientated in a flow by Hookean dumbbells, thus limiting the model to low shear rate flows. The extra-stress tensor $\boldsymbol{\tau}$ in Eq. (6.14) may be written as the sum of a Newtonian viscous stress tensor and an elastic stress tensor $\boldsymbol{\tau_E}$

(represents the contri- bution to the extra-stress due to the erythrocytes.)

$$\boldsymbol{\tau} = 2\mu \boldsymbol{D}(\boldsymbol{u}) + \boldsymbol{\tau_E} \tag{15}$$

Comparison of predictions of constitutive models with experimental data

In a study in 1980 by Easthope and Brooks (...) . The model of Walburn and Schneck resulted in the closest fit. The predictions of the Walburn and Schneck model have been compared with those of a Newtonian fluid, Casson model and Bingham model for laminar flow through a straight tube under flow conditions bearing some similarity to those that exist in the femoral artery by Rodkiewicz et al (..) . The Walburn and Schneck model was seen to give markedly different results from the other models in pulsatile flow and these were stated as being in conformity with some experimental results [289]. The authors noted that the constitutive model of Walburn and Schneck was developed for low shear rates, however, and was not valid for certain shear rate regimes seen in their pulsatile flow simulations

Details of a recent comparison between a Newtonian, Casson, power-law and Quemada [412] model are to be found in the paper of Neofytou [348]. The author considered the case of channel flow where part of one of the channel walls was forced to oscillate laterally, this being claimed to reproduce some flow phenomena seen under realistic arterial conditions. The Casson and Quemada models 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

A full description of all the comparisons that have been performed with the model of Owens may be found in [141]. Other viscoelastic models have already been used with some success for the simulation of this flow. For exam- ple, the pressure field predictions of the viscoelastic model of Anand and Rajagopal [10] were in reasonable agreement with the data of Thurston [504] for oscillatory tube flow and comparisons were also made between the experi- mental data and the results from a model of Yeleswarapu [548,549] and gener- alised Oldroyd-B and Maxwell models. Neither of the generalised models was found to give satisfactory results for oscillatory flows, however.

Conclusion

the mate- rial properties of flowing human blood, and in particular its shear viscosity, elasticity and thixotropy may be explained in terms of the complex evolving microstructure, and especially that of the de- forming and migrating red blood cells in their different states of aggregation. We would suggest, therefore, that the most promising rheological models to date are those developed from an underlying microstructure similar to that of blood (albeit necessarily simpli- fied). The retention of sufficient detail at the microscopic level may be hoped to translate into faithful reproduction of some of the complex characteristics of blood, particularly those associated with its thixotropic nature

Secondly, when we write of the desirability of sufficient detail at the microstructural level being retained in rheological models we mean just sufficient. Although we want to be able to successfully predict non-Newtonian effects in, say, an aneurysm we would like any reasonable model to collapse to the Navier-Stokes equations (with some suitable apparent viscosity) in bulk arterial flow, for example. A model that is unnecessarily complicated or costly, may have a sound rheological foundation but has little chance of attracting the attention of the medical community and therefore of being implemented in practical situations

Thirdly, and finally, the development of stable, accurate and affordable numerical methods tailored to the new set of constitutive equations for blood is of the utmost importance. For example, proper account must

be taken of the mathematical type of the system of equations, and the possible addition of elastic stress variables make the use of parallelisable algorithms even more crucial than they are in present day CFD Newtonian solvers. Faster large-scale computing platforms are open- ing up new possibilities in simulation and visualisation.

2.2 A REVIEW ON RHEOLOGY OF NON-NEWTONIAN PROPERTIES OF BLOOD

INTRODUCTION

Most commonly, the viscosity (the measure of a fluid's ability to resist gradual deformation by shear or tensile stresses) of non-Newtonian fluids is dependent on the shear rate or shear rate history. Some non-Newtonian fluids with shear- independent viscosity, however, still exhibit normal stress-differences or other non- Newtonian behavior. [...]

Blood is a complex fluid with non-Newtonian characteristics, it has a shear-thinning behavior [3] and often exhibits a ***yield stress (viscoplasticity)*** *[4-6] with* ***potential history effects (thixotropy)*** *[7]. [...]The rheological complexity of blood is attributed to its constituents. Rheologically, blood is primarily characterized as a concentrated suspension of elastic, deformable red blood cells (RBCs). However, it also contains other ingredients such as leukocytes and platelets within plasma.* ***Yield stress is an important characteristic of blood rheology and an essential component of its non-Newtonian nature****. Experimental evidence for its association with blood has been provided in many investigations. [...]*

This may also explain a possible controversy about the thixotropic nature of blood [13] as the thixotropic-like behavior may be explained by other non-Newtonian characteristics of blood. Thixotropy is more pronounced at low shear rates with a long-time scale. The effect, however, seems to have a less important role in blood than other non-Newtonian effects such as shear thinning [14], and this could partly explain the limited amount of studies dedicated to this property. The thixotropic behavior of blood is very sensitive to blood composition and hence it can demonstrate big variations between different individuals and under different biological conditions.

RHEOLOGY OF BLOOD

Blood behaves like a non-Newtonian fluid whose viscosity varies with shear rate. The non-Newtonian characteristics comes from the presence of various cells in the blood that make blood a suspension of particles. When the blood begins to move, these particles (or cells) interact with plasma and among themselves. Hemorheologic parameters of blood include whole blood viscosity, plasma viscosity, red cell aggregation, and red cell deformability (or rigidity). From a biological point of view, blood can be considered as a tissue comprising various types of cells (i.e., RBCs, WBCs, and platelets) and a liquid intercellular material (i.e., plasma). From a rheological point of view, blood can be thought of as a two-phase liquid; it can also be considered as a solid-liquid suspension, with the cellular elements being the solid phase.

DETERMINANTS OF BLOOD VISCOSITY

Theory that completely accounts for the viscous properties of blood, and some of the key determinants have been identified: The ***four main determinants of whole blood viscosity are (1) plasma viscosity, (2) hematocrit, (3) RBC deformability and aggregation, and (4) temperature****. The first three factors are parameters of physiological concern because they pertain to changes in whole blood viscosity in the body.* ***The second and third factors, hematocrit and RBC (red blood cells) aggregations, are the main contributors to the non-Newtonian characteristics of shear-thinning viscosity and yield stress.***

YIELD STRESS

In addition to non-Newtonian viscosity, blood also exhibits a yield stress. The source of the yield stress is the presence of cells in the blood, particularly red cells. When such a huge amount of red cells of 8-10 microns in diameter is suspended in plasma, cohesive forces among the cells are not negligible. ***The forces existing between particles are van der Waals-London forces and Coulombic forces . Hence, in order to initiate a flow from rest, one needs to have a force that is large enough to break up the particle-particle links among the cells****. However, blood contains red cells and still moves relatively easily. The healthy red cells behave like liquid drops because the membranes of red cells are so elastic and flexible. Note that in a fluid with no suspended particles, the fluid starts to move as soon as an infinitesimally small amount of force is applied.* ***Such a fluid is called a fluid without yield stress. Examples of fluid with no yield stress include water****. Examples of fluids having yield stress include blood, ketchup, salad dressings, grease, paint, and cosmetic liquids.*

The magnitude of the yield stress of human blood (...) is almost independent of temperature in the range of 10-37 degree

Blood shows a Newtonian fluids character when it flows through larger diameter arteries at high shear rates, but it exhibits a remarkable non-Newtonian behavior when it flows through small diameter arteries at low shear rates. Moreover, there is an increase in viscosity of blood at low rates of shear as the red blood cells tend to aggregate into the Rouleaux form. ***Rouleaux form behaves as a semi-solid along the center forming a plug flow region. In the plug flow region, we have a flattened parabolic velocity profile rather than the parabolic velocity profile of a Newtonian fluid. This behavior can be modeled by the concept of yield stress.***

Casson fluid model

is a non-Newtonian fluid with yield stress, which is widely used for modeling blood flow in narrow arteries. Many researchers have used the Casson fluid model for mathematical modeling of blood flow in narrow arteries at low shear rates. It has been demonstrated by Blair [28] and Copley [29] that the Casson fluid model is adequate for the representation of the simple shear behavior of blood in narrow arteries. Casson examined the validity of the Casson fluid model in his studies pertaining to the flow characteristics of blood and reported that at low shear rates, the yield stress for blood is nonzero

The yield stress characteristic of blood seems to vanish or become negligible when hematocrit level falls below a critical value. Yield stress contributes to the blood clotting following injuries and subsequent healing, and may also contribute to the formation of blood clots (thrombosis) and vessel blockage in some pathological cases such as strokes. The magnitude of yield stress and its effect could be aggravated by certain diseased states related to the rheology of blood, like polycythemia vera, or the structure of blood vessels such as stenosis.

THIXOTROPY

The phenomenon of thixotropy in a liquid result from the microstructure of the liquid system. Thixotropy may be explained as a consequence of aggregation of suspended particles. If the suspension is at rest, the particle aggregation can form, whereas if the suspension is sheared, the weak physical bonds among particles are ruptured, and the network among them breaks down into separate aggregates that can disintegrate

further into smaller fragments [40]. After some time at a given shear rate, a dynamic equilibrium is established between aggregate destruction and growth, and at higher shear rates, the equilibrium is shifted in the direction of greater dispersion. The relatively long time required for the microstructure to stabilize following a rapid change in the rate of flow makes blood thixotropy readily observable [...] At high shear rates, structural change occurs more rapidly than at low shear rates.

BLOOD VISCOSITY MEASUREMENT

Blood viscosity is mainly determined by the hematocrit and varies with the shear rate as a non-Newtonian fluid [44,

Lee et al. [54] studied the applicability of ***two non-Newtonian constitutive models (Casson and Herschel-Bulkley models) in the determination of the blood viscosity and yield stress using a pressure-scanning microfluidic hemorheometer****. The present results were compared with the measurements through a precision rheometer (ARES2). For a Newtonian fluid (standard oil), the two constitutive models showed excellent agreement with a reference value and the measurement of ARES2. For human blood as a non-Newtonian fluid, both the Casson and Herschel-Bulkley models exhibited similar viscosity results over a range of shear rates and showed excellent agreement with the ARES2 results. The Herschel-Bulkley model yielded a slightly higher value than other results at low shear rates, which may be due to the relatively high value of the yield stress. The yield stress values for whole blood were 14.4 mPa for the Casson model and 32.5 mPa for the Herschel-Bulkley model, respectively.* ***Thus, their study showed that the Casson model would be better than the Herschel-Bulkley model for representing the non-Newtonian characteristics of blood viscosity [54].***

Kang et al. presented the first experimental work on the viscosity measurement of adult zebrafish whole blood using a capillary pressure-driven microfluidic viscometer. After the device calibration with water, the viscosity measurement of human whole blood was performed and in good agreement with published data, demonstrating the reliability of the device. ***Power law and Carreau-Yasuda rheological models were used to model the non-Newtonian behaviors of the human*** *and zebrafish blood [56].*

This result indicates that blood viscosity is likely to be more affected by blood cell particle numbers than by blood cell volume. Although this comparison has not been addressed in human clinical studies, a previous animal study demonstrated that the blood cell count had a stronger influence on blood viscosity than the hematocrit [57].

HEAT TRANSFER OF BLOOD FLOW

The effects of flow parameters namely Grashof number (Gr), Prandtl number (Pr), heat source parameter (N), Hartmann number (M) and decay parameter (λ) on the velocity and heat functions have been observed

CONCLUSION

In this paper, rheological characteristics of blood were studied. As referred to in previous work, blood is a complex fluid with non-Newtonian characteristics. It often represents a yield stress (viscoplasticity) and has a shear-thinning behavior and due to the pulsative nature of the blood flow, it shows a thixotropy treatment. Blood has four main determinants including plasma viscosity, hematocrit, red blood cell deformability, and temperature. Blood shows a Newtonian fluids character when it flows through larger

diameter arteries at high shear rates, but it exhibits a remarkable non-Newtonian behavior when it flows through small diameter arteries at low shear rates. Despite the fact that thixotropy is a transient property, due to the pulsative nature of the blood flow the thixotropic effects may have long term impact on the blood circulation. It should be remarked that time dependent effects whether thixotropic or viscoelastic in nature, should be expected in blood flow due to the pulsatility of blood flow and the rapid change in the deformation conditions during blood circulation. Modeling of heat transfer in the body can be used in surgery, especially open-heart surgery, as well as in making artificial blood vessels.

2.3 Methods of Blood Flow Modelling

Hemorheology

the science of deformation and flow of blood and its formed elements. This field includes investigations of both macroscopic blood properties using rheometric experiments as well as microscopic properties in vitro and in vivo.

Blood components

Blood is a concentrated suspension of several formed cellular elements, red blood cells (RBCs or erythrocytes), white blood cells (WBCs or leukocytes) and platelets (thrombocytes), in an aqueous polymeric and ionic solution, the plasma, composed of water and particles, namely, electrolytes, organic molecules, numerous proteins (albumin, globulins and fibrinogen) and waste products.
[...] Normal erythrocytes are biconcave discs with a mean diameter of 6 to 8 μm and a maximal thickness of 1.9 μm.

Non-Newtonian properties of blood

The mechanical properties of blood should be studied by considering a fluid containing a suspension of particles. A fluid is said to be Newtonian if it satisfies the Newtons law of viscosity (the shear stress is proportional to the rate of shear and the viscosity is the constant of proportionality). Blood plasma, which consists mostly of water, is a Newtonian fluid. However, the whole blood has complex mechanical properties which become particularly significant when the particles size is much larger, or at least comparable, with the lumen size. ***In this case, which happens at the microcirculation level (in the small arterioles and capillaries) blood cannot be modelled has a homogeneous fluid and it is essential to consider it as a suspension of blood cells (specially RBCs) in plasma.***

Otherwise, depending on the size of the blood vessels and the flow behaviour, it is approximated as a Navier-Stokes fluid or as a non-Newtonian fluid. ***Here we assume that all macroscopic length and time scales are sufficiently large compared to length and time scales at the level of the individual erythrocyte so that the continuum hypothesis holds.***

Viscosity of blood

In general blood has higher viscosity than plasma, and when the hematocrit rises, the viscosity of the suspension increases and the non-Newtonian behaviour of blood becomes more relevant, in particular at ***very low shear rates****. The apparent viscosity increases slowly until a shear rate less than 1 s-1 where it rises markedly. The reason for this is that at low shear rates the erythrocytes have the ability to form a primary aggregate structure of rod shaped stacks of individual cells called* ***rouleaux****, that align to each other and form a secondary structure consisting of branched three-dimensional (3D) aggregates [118]. It has been experimentally observed that rouleaux will not form if the erythrocytes have been hardened or in the absence of fibrinogen and globulins (plasma proteins) [30]. (In fact, suspensions of erythrocytes in plasma demonstrate a strong non-Newtonian behaviour whereas when they are in suspension in physiological saline (with no fibrinogen or globulins) the behaviour of the fluid is Newtonian). For standing blood subjected to a shear stress lower than a critical value, these 3D structures*

can form and blood exhibits yield stress and resists to flow until a certain force is applied. This can happen only if the hematocrit is high enough.

***At moderate to high shear rates**, RBCs are dispersed in the plasma and the properties of the blood are influenced by their tendency to align and form layers in the flow, as well as to their deformation. The effect of RBC deformability on the viscosity of suspensions was clearly shown in*

***For shear rates above 400 s-1**, the RBCs lose their biconcave shape, become fully elongated and are transformed into ellipsoids with major axes parallel to the flow direction. The tumbling of the RBCs is absent, there are almost no collisions, and their contours change according to the tank-trading motion of the cells membranes about their interior. The apparent viscosity decreases and this becomes more evident in smaller than in larger vessels. This happens with vessels of internal diameter less than 1 mm and it is even more pronounced in vessels with a diameter of 100 to 200 μm.The geometric packing effects and radial migration of RBCs can act to lower the hematocrit adjacent to the vessel wall and contribute to decrease the blood viscosity. This is known as the **Fahraeus-Lindqvist effect**. **Plasma skimming** is another effect that results in diminishing the viscosity when blood flows into small lateral vessels compared with the parent vessel.*

Plasma skimming: The natural separation of red blood cells from plasma at bifurcations in the vascular tree, dividing the blood into relatively concentrated and relatively dilute streams.

As a consequence of this behaviour we can say that one of the non-Newtonian characteristics of blood is the shear thinning viscosity. This happens in small size vessels or in regions of stable recirculation, like in the venous system and parts of the arterial vasculature where geometry has been altered and RBC aggregates become more stable, like downstream a stenosis or inside a saccular aneurysm. However, in most parts of the arterial system, blood flow is Newtonian in normal physiological conditions

Constitutive Models

*Simplest constitutive model for **incompressible viscous fluids based on the assumption that the extra stress tensor is proportional to the symmetric part of the velocity gradient***

$$\boldsymbol{\tau} = 2\mu \boldsymbol{D}(\boldsymbol{u})) \tag{16}$$

with rate of deformation tensor

$$D_{ij} = \frac{1}{2}(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}) \quad i,j = 1,...3 \tag{17}$$

The substitution of $\boldsymbol{\tau}$ in the equations of the conservation of linear momentum and mass (or incompressibility condition) for isothermal flows given by well-known Navier-Stokes equations for an incompressible viscous fluid

As already discussed, this set of equations is commonly used to describe blood flow in healthy arteries. However, under certain experimental or physiological conditions, particularly at low shear rates, blood exhibits relevant non-Newtonian characteristics and more complex constitutive models need to be used.

*In this case, we require a more general constitutive equation relating the state of stress to the rate of deformation which satisfies invariance requirementts. One of the simplest is the special class of **Reiner-Rivlin fluids, called generalised Newtonian fluids**, for which*

$$\boldsymbol{\tau} = 2\mu(\dot{\gamma}) \boldsymbol{D}(\boldsymbol{u})) \tag{18}$$

where $mu(\dot{\gamma})$ is a shear dependent function and $\dot{\gamma}$ is the shear rate (a measure of the rate of deformation) defined by

$$\dot{\gamma} = \sqrt{2tr(\boldsymbol{D}(\boldsymbol{u}))^2)} = \sqrt{-4\Pi_D} \tag{19}$$

Here Π_D denotes the second principal invariant of the tensor $\boldsymbol{D}$, given by

$$\Pi_D = \frac{1}{2}((tr\boldsymbol{D})^2 - tr\boldsymbol{D}^2) \tag{20}$$

A simple example of a generalised Newtonian fluid is the power-law fluid, for which the viscosity function is given by

$$\mu(\dot{\gamma}) = K\dot{\gamma}^{n-1} \tag{21}$$

the positive constantts n and K being the power-law index and the consistency, respectively. This model includes

1. *as a particular case, the constant viscosity fluid (Newtonian) when $n = 1$.*
2. *For $n < 1$ it leads to a monotonic decreasing function of the shear rate (shear thinning fluid)*
3. *for n ¿ 1 the viscosity increases with shear rate (shear thickening fluid).*

The shear thinning power-law model is often used for blood, due to the analytical solutions easily obtained for its governing equations, but it predicts an unbounded viscosity at zero shear rate and zero viscosity when $\dot{\gamma} \longrightarrow \infty$, which is unphysical

***Extensions of the power-law model is due to Walburn and Schneck** who considered the dependence of the viscosity on the hematocrit (H_t) and total protein minus albumin (TPMA) in the constants n and K, based on nonlinear regression analysis*

$$K = C_1 exp(C_2 H_t), \qquad n = 1 - C_3 H_t \tag{22}$$

Comparison between different models see original paper and cited paper!

Viscosity functions with bounded and non-zero limiting values of viscosity can be written in the general form or

$$\mu(\dot{\gamma}) = \mu_\infty + (\mu_0 - \mu\infty)F(\dot{\gamma}) \tag{23}$$

, in non-dimensional form as

$$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu\infty} = F(\dot{\gamma}) \tag{24}$$

Here, (μ_0 and $\mu\infty$) are the asymptotic viscosity values at zero and infinite shear rates and $F(\dot{\gamma})$ is a shear dependent function, satisfying the natural limit condition, i.e. goes to 1 for strain rate to zero and goes to 0 if strain rate goes to infinity

Different choices of the function $F(\dot{\gamma})$ correspond to different models for blood flow, with material constants quite sensitive and depending on a number of factors including hematocrit, temperature, plasma viscosity, age of RBCs, exercise level, gender or disease state.

Model	$F(\dot{\gamma})$	Material constants for blood
Powell-Eyring	$\frac{sinh^{-}1(\lambda\dot{\gamma})}{\lambda\dot{\gamma}}$	$\lambda = 5.383s$
Cross	$\frac{1}{1+(\lambda\dot{\gamma})^m}$	$\lambda = 1.007s, m = 1.028$
Modified Cross	$\frac{1}{1+((\lambda\dot{\gamma})^m)^a}$	$\lambda = 3.736s, m = 2.406, a = 0.254$
Carreau	$(1+(\lambda\dot{\gamma})^2)^{\frac{n-1}{2}}$	$\lambda = 3.313s, n = 0.3568$
Carreau-Yasuda	$(1+(\lambda\dot{\gamma})^a)^{\frac{n-1}{a}}$	$\lambda = 1.902s, n = 0.22, a = 1.25$

Table 1: Material constants for various generalised Newtonian models for blood with $\mu_0 = 0.056$Pa.s, $\mu_\infty = 0.00345$Pa.s

Viscoelasticity and thixotropy of blood Viscoelastic

Viscoelastic fluids *are viscous fluids which have the ability to store and release energy. The viscoelasticity of blood at normal hematocrits is primarily attributed to the reversible deformation of the RBCs 3D microstructures [131].* ***Elastic energy is due to the properties of the RBC membrane which exhibits stress relaxation*** *[42] and the bridging mechanisms within the 3D structure. Moreover, the experimental results of Thurston* ***imply that the relaxation time depends on the shear rate****. The reader is referred to [131] for a review of the dependence of blood viscoelasticity on factors such as temperature, hematocrit and RBC properties.* ***In view of the available experimental evidence, it is reasonable to develop non-Newtonian fluid models for blood that are capable of shear thinning and stress relaxation, with the relaxation time depending on the shear rate. To date, very little is known concerning the response of such fluids****. In fact, viscoelastic properties are of relatively small magnitude and they have generally only been measured in the context of linear viscoelasticity. By shear rates of the order of 10 s-1 the elastic nature of blood is negligible as evidenced by a merging of the oscillatory and steady flow viscosities.* ***However, there is a need to consider the finite viscoelastic behaviour of blood, if viscoelastic constitutive equations are used to model blood in the circulatory system***

A number of ***nonlinear viscoelastic constitutive models for blood are now available but because of their complexity we will avoid presenting the mathematical details here****, providing instead a summary of the relevant literature. One of the simplest rate type models accounting for the viscoelasticity of blood is the* ***Maxwell model***

$$\tau + \lambda_1 \frac{\partial \tau}{\partial t} = 2\mu D \tag{25}$$

where λ_1 is the relaxation time and $\frac{\partial \cdot}{\partial t}$ stands for the so-called convected derivative, a generalisation of the material time derivative, chosen so that $\frac{\partial \tau}{\partial t}$ is objective under a superposed rigid body motion and the resulting second-order tensor is symmetric[114]

A more general class of rate type models, includes the ***Oldroyd-B*** *models defined by*

$$\tau + \lambda_1 \frac{\partial \tau}{\partial t} = 2(\mu D + \lambda_2 \frac{\partial D}{\partial t}) \tag{26}$$

) where the material coefficient λ_2 denotes the retardation time (Verzoegerungszeit) and is such that $0 \leq \lambda_2 < \lambda_1$. ***the Oldroyd type fluids can be considered as Maxwell fluids with additional viscosity****. These models contain the previous model as a particular case.Thurston [129], was among the earliest to recognise the viscoelastic nature of blood and that the viscoelastic behaviour is less prominent with increasing shear rate. He proposed a generalised Maxwell model that was applicable to one dimensional flow*

simulations (see section 3) and observed later that, beyond a critical shear rate, the nonlinear behaviour is related to the microstructural changes that occur in blood [130]. Thurstons work was suggested to be more applicable to venous or low shear unhealthy blood flow than to arterial flows. Recently, a generalised Maxwell model related to the microstructure of blood, inspired on the behaviour of transient networks in polymers, and exhibiting shear thinning, viscoelasticity and thixotropy (defined below), has been derived

Other viscoelastic constitutive models of differential type, suitable for describing blood rheology have been proposed in the recent literature. ***The empirical three constant generalised Oldroyd -B model studied in [149] belongs to this class. It has been obtained by fitting experimental data in one dimensional flows and generalising such curve fits to three dimensions. This model captures the shear thinning behaviour of blood over a large range of shear rates but it has some limitations, since the relaxation times do not depend on the shear rate, which does not agree with experimental observations****. The model developed by Anand and Rajagopal [9] in the general thermodynamic framework stated in [113] includes relaxation times depending on the shear rate and gives good agreement with experimental data in steady Poiseuille and oscillatory flow*

Another important property of blood is its ***thixotropic behaviour****, essentially due to the fact that the formation of the three-dimensional microstructure and the alignment of the RBCs are not instantaneous. Essentially, we refer to thixotropy as the dependence of the material properties on the time over which shear has been applied. This dependence is due to the finite time required for the build-up and breakdown of the 3D microstructure, elongation and recovery of RBCs and the formation and breakdown of layers of the aligned RBCs [13]*

Yield stress of blood

The behaviour of many fluids at low shear stress, including blood, has led researchers to believe in the existence of a critical value of stress below which the fluid will not flow. This critical stress level, called the yield value or yield, is typically treated as a constant material property of the fluid. [...] Reported values for the yield stress of blood have a great variation ranging from 0.002 to 0.40 dynes/cm^2 (...) ***Rather than treating the yield stress as a constant, it should be considered as a function of time and linked to thixotropy, as later proposed by other researchers [89].***

Yield stress models can be useful to model blood flow in low shear rate regions*. Yield stress materials require a finite shear stress τ_Y (the yield stress) to start flowing. A relatively simple, and physically relevant yield criterion is given by*

$$\sqrt{|\Pi|_\tau} = \tau_Y \tag{27}$$

where $\sqrt{|\Pi|_\tau}$ is the second invariant of the extra stress tensor, τ (see (1.5)). Therefore, for $\sqrt{|\Pi|_\tau} < \tau_Y$, (1.9) fluid will not flow!

The most common yield stress model for blood is the ***Casson model*** *([119]) which, in simple shear flow, has the form*

$$\sqrt{|\Pi|_\tau} < \tau_Y \Rightarrow D = 0 \tag{28}$$

$$\sqrt{|\Pi|_\tau} \geq \tau_Y \Rightarrow \begin{cases} D &= \frac{1}{2\mu_n}(1 - \frac{\sqrt{\tau_Y}}{\sqrt{|\Pi|_\tau}})^2\tau \ , \\ \tau &= 2(\sqrt{\mu_n} + \frac{\sqrt{\tau_Y}}{\sqrt[4]{4|\Pi|_\tau}})^2 \end{cases} \tag{29}$$

The Newtonian constitutive equation is a special case of (1.10) for τ_Y equal to zero, in which case, μ_N is the Newtonian viscosity. The Casson fluid behaves rigidly until (1.9) is satisfied, after which it displays a shear thinning behaviour.

*Other yield stress models like **Bingham** or **Herschel-Bulkley models** are also used for blood (see e.g. [114]) as well as the **constitutive model developed by Quemada** [112] using an approach, with the apparent viscosity μ given by*

$$\mu = \mu_f(1 - \frac{1}{2}\frac{k_0 + k_\infty\sqrt{\dot{\gamma}/\dot{\gamma_C}}}{1 + \sqrt{\dot{\gamma}/\dot{\gamma_C}}}\phi)^{-2} \tag{30}$$

where μ_F, ϕ and$\dot{\gamma_C}$ are the viscosity of the suspending fluid, the volume concentration of the dispersed phase and a critical shear rate

2.4 Recent advances in blood rheology: a review

Introduction

Experimentally, blood has been confirmed to demonstrate a variety of non-Newtonian rheological characteristics, including pseudoplasticity, viscoelasticity, and thixotropy. New rheological experiments and the development of more controlled experimental protocols on more extensive, broadly physiologically characterized, human blood samples demonstrate the sensitivity of aspects of hemorheology to several physiological factors. For example, at high shear rates the red blood cells elastically deform, imparting viscoelasticity, while at low shear rates, they form rouleaux structures that impart additional, thixotropic behavior.

As the volume fraction of RBCs (hematocrit) by far exceeds that of any other component (see also Table 1), it is common to consider blood as a suspension of flexible RBCs in an otherwise Newtonian fluid, as will be discussed. Complex interactions between RBCs result in aggregates (rouleaux) that can grow to form a temporary network at low shear rates,5 which results in a significantly complex rheological behavior

Consequently, hemorheology is characterized by a shear thinning viscosity, a general viscoelastic response to transient flow deformations and a non-zero yieldstress with associated thixotropy . see, for example, a recent review2 and references therein

Models derived from these advances range from simpler, generalized Newtonian, approaches, suitable mostly for steady-state shear-dominated flows, to thixotropic, elastoviscoplastic models, appropriate to study bloods complex transient rheological behavior. The emphasis of this review is continuum models to describe bulk blood rheology, although important connections to microscopic and multiscale models are also mentioned

Hemorheology characteristics

most obvious non-Newtonian characteristic of blood rheology is its shear thinning in steady shear flow (...) However, with time, people discovered that blood rheology exhibits additional more complex rheological characteristics, including viscoplasticity, viscoelasticity and thixotropy.

TABLE with various quantities that can be used to characterize various aspects of hemorheology, such as various measures for limiting values (at zero and high shear rates) of blood viscosity, and its contribution from plasma and rouleaux, characterizing shear thinning, yield stress characterizing viscoplasticity, and three typical characteristic times useful to characterize two separate components of viscoelasticity (originating from the free RBC deformation, rouleaux aggregates) and thixotropy associated with rouleaux formation due to Brownian motion.

In addition to a pronounced shear thinning behavior, the presence of rouleaux in blood also gives rise to viscoelasticity and thixotropy. Due to the weak viscoelasticity of blood and a transition to nonlinear behavior at low strain amplitudes, the linear viscoelastic behavior of blood is typically difficult to measure. Thus, rheological techniques, such as large amplitude oscillatory shear (LAOS), which measure the thixotropy and viscoelasticity simultaneously, are more commonly used.27 At low shear rates, where the rouleaux are present, there is considerably more elasticity present in the sample; whereas, at high shear rates, the elasticity present is more representative of that of the isolated RBCs. The thixotropic behavior of blood arises from the structural evolution of the rouleaux which introduces a thixotropic time scale.

The complex rheological properties of blood are often reported in an (overly) simplified manner by a few characteristic metrics. One such metric which governs the low shear behavior of blood is the yield stress.

The yield stress of blood is typically very small, on the order of 1 mPa, and consequently difficult to measure, and can be easily missed if one is not careful to avoid the wall slip phenomenon.29 The most common method for determining

The main physiological determinants of whole blood rheology tend to be the hematocrit and the fibrinogen concentration, with the latter affecting the aggregation tendency of the rouleaux. Various authors suggest that the low shear behavior of blood is dependent on both these parameters, with aggregation occurring only above a certain critical hematocrit

Experimental methods Rheometry

...

Constitutive blood modeling

From the four non-Newtonian characteristics of blood rheology, namely shear thinning, yield stress, thixotropy and viscoelasticity, the first two can be easily captured through the use of a variety of generalized non-Newtonian equations

Of these, a special mention here is the historic Casson model (eqn (2)),47 both because this was the workhorse model for describing blood viscosity,21,84 but primarily because it is the one for which we have the most extensive knowledge of the parametric dependence of the model parameters on important physiological parameters, such as the hematocrit and the fibrinogen concentration

In its more natural form the Casson model is cast as a linear dependence of the square root of the shear stress with respect to the shear rate,47 giving rise to the following expression for the equivalent generalized shear viscosity

A major breakthrough in that respect has been the validation of the previously proposed data collection protocol and further elaboration on a systematic steady but also transient shear experimental protocol by Horner et al.49 and the availability of a set of well documented experimental data on both human and several animal species blood see also sepa-rate section in this review on Comparative hemodynamics and Hemorheology. This recent work has led to more accurate data that not only advances our knowledge about non-Newtonian blood rheology in transient flows, which is not captured of course through inelastic, generalized Newtonian approaches, but also suggests small, but important, corrections to the Casson model predictions and the square root law even regarding the steady state shear viscosity.13,52

Thixotropic/elastoviscoplastic models for blood

Generalized Newtonian models are computationally inexpensive to implement but cannot predict accurately transient (thixotropic/ hysteretic) changes in the viscosity which are relevant as blood flows naturally under pulsatile conditions. To better account for the transient effects, a viscoelastic model can be used

One example of this is the Anand-Kwack-Masud (AKM) model which is a generalization of the Oldroyd-B

model

$$\boldsymbol{\sigma} = G\boldsymbol{B} + 2\eta_\infty \boldsymbol{D} \tag{31}$$

$$\overset{\triangledown}{\boldsymbol{B}} = (\frac{G}{\eta_0 - \eta_\infty})(\frac{tr(\boldsymbol{B})}{3})^m(\boldsymbol{B} - \frac{3}{tr(\boldsymbol{B^{-1}}\boldsymbol{I})} \tag{32}$$

where σ is the stress tensor, G is an elastic modulus, $\boldsymbol{B}$ is the left Cauchy-Green stretch tensor, $\boldsymbol{D}$ is rate of strain tensor, the superimposed inverted triangle denotes the upper-convected time derivative, m is a power law index, and I is the unit tensor. ***Viscoelastic models similar to this approach are advantageous for modeling blood flow as they can account for elasticity in the sample and can predict non-shear components of the stress tensor. How- ever, they are typically unable to capture thixotropic effects that blood demonstrates associated with the structural evolution***

This parameter is then connected to a description describing the contribution to the stress by the rouleaux structures. Notable in this respect, in its pioneering description that unifies thixotropy and viscoelasticity, is a model by Sun and De Kee that uses a generalized Maxwell viscoelastic model with viscoelastic parameters that depend on a structure parameter governed by a separate evolution equation

One of the most successful thixotropic models for blood is the Horner-Armstrong-Wagner-Beris (HAWB) model52 which uses this approach to describe the rouleaux contribution to the shear stress

... ...

Microscopic/mesoscopic models of blood

In reality, the inherent complexity of blood, can only be captured well through microscopic modeling. Blood, not only involves a concentrated suspension of deformable, elastic, and aggregating RBCs, but also a host of other ingredients from platelets and WBCs to various proteins Moreover, all of these interact in a complicated way. This complicated structure is the reason for bloods complex rheology, not only characterized by a non-zero yield stress and shear thinning but also pronounced history effects, i.e., thixotropy, as fully discussed above.

efforts have therefore been made to reconstruct the non- Newtonian characteristic of blood from micromechanical models based on first principles (...) Adjustable parameters to describe RBC behavior are still necessary in microscopic as well as mesoscopic level just as at the macro-scopic level discussed above.

More recently, simulations became much more sophisticated, for example, taking into account in order to model the aggregation process the role of fibrinogen and even including effects of pathological conditions like type 2 diabetes mellitus135 and hyperviscosity based on cell interactions, cell stiffness and hematocrit.136 Especially important is the use of microscopic/mesoscopic models in the evaluation of blood hemostasis and thrombosis -see recent reviews on the subject.

There are several benefits that can so far be extracted from microscopic blood flow simulations. First, there is theoretical confirmation on the inhomogeneities generated in the flow due to the finite particle sizes and their elastic properties, interparticle interaction forces (leading also to aggregation), and wall exclusion and hydrodynamic forces effects. Second, they can generate important detailed information necessary in building and validating coarser scale models. Third, they can eventually make the connection to the underlying biology

Multiscale models

Multiscale models attempt to bridge the gap between the nanoscale, mesoscale and macroscale dynamics while retaining relevant information at smaller length scales. Systems such as blood, multicomponent, involving a concentrated suspension of deformable RBC dominated by strong interactions between themselves and several of the multitude of the other present components, have such a degree of complexity that makes a multiscale approach particularly advantageous. advantageous. Before selecting the approach for multiscale modeling, it is important to consider the flow regime, geometry as well available computational resources.

2.5 A critical review on blood flow in large arteries; relevance to blood rheology, viscosity models, and physiologic conditions

The arterial blood flow in the human body is typically a multiphase non-Newtonian pulsatile flow in a tapered elastic duct with the terminal side and/or small branches.The pulsatile flow is an unsteady flow in which resultant flow is composed of a mean and a periodically varying time-dependent component. Pulsatile flow is responsible for submissive effect on time-dependent viscoelastic and thixotropy behavior of blood

Blood composition and structure

Blood composition and structure play a vital role in blood rheology. Blood consists of a suspension of elastic particulate cells in a liquid known as plasma (..) Potential non-Newtonian properties of plasma were considerable debate until the early 1960 (Zydney et al., 1991), but recent studies have demonstrated that plasma is a Newtonian fluid with a viscosity which is a function of temperature

The aggregatable and deformable nature of the red RBCs plays significant roles in blood rheology. RBC aggregation causes a large increase in viscosity at low shear rates. The size of RBC aggregation is a function of RBC concen- tration and shear rate (Zydney et al., 1991). The existence of aggregation also depends on the presence of fibrinogen and globulin proteins in plasma (Fung, 1993). When shear rate tends to zero, RBCs become one big aggregate, which then behaves like a solid. As the shear rate increases, RBCs aggregates tend to be broken up and the structure becomes a suspension of a cluster of RBCs aggregates in plasma. These aggregates are in turn formed from smaller units called rouleaux as shown. As the shear rate more increases, the average number of RBCs in each rouleaux decreases. If the shear rate is larger than a certain critical value, the rouleaux are broken up into indi- vidual cells. At subcritical shear rates, the RBCs in each rouleaux maintain their rest-state equilibrium shape, bicon- cave discoid shape. If the shear rate is supercritical, the RBCs are dispersed in plasma separately and tend to become elongated and line up with the streamlines (see

The difference between the NP and NA curves indicates the effect of cell aggregation, whereas that between NA (suspended in albumin (leads to lack of other proteins in solution which prevents aggregation)) and HA (hardened RBCs in albumin) indicates the effect of cell deformation. Aggregation of red cells at low shear rates leads to increase of viscosity. Red cells elongation and orientation at high shear rates lead to decrease of viscosity further

the blood viscosity is dependent on the physiological flow conditions of blood and the blood composition properties such as hematocrit, temper- ature, shear rate, cell aggregation, cell shape, cell defor- mation and orientation. All of these observed dependencies should be formulated and then systematically introduced into some blood viscosity models for use in CFD analysis of blood flow. The review of the present viscosity models discussed in the following section however showed that; the effects of cell aggregation, cell shape, cell deformation, and cell orientation have not clearly reflected in the vis- cosity models, although these models considers the effects of hematocrit or cell concentration, shear rate, and tem- perature. However, numerical studies on RBC behaviors give a hope for transferring available knowledge of micro- scopic hemodynamic and hemorheological behaviors to a blood viscosity mode

Blood viscosity models

Experimental investigations over many years showed that blood flow exhibits non-Newtonian behavior such as shear thinning, thixotropy, viscoelasticity, and yield stress. Its rheology is influenced by many factors including plasma viscosity (Baskurt and Meiselman, 2003), align- ment of RBCs (Baskurt and Meiselman, 1977), level of RBC aggregation and deformability (Chien, 1970), fibrin- ogen (Chien et al, 1970), flow geometry and size (Thurston and Henderson, 2006), rate of shear, hematocrit, male or female, smoker or non-smoker, temperature, lipid loading, hypocaloric diet, cholesterol level, physical fitness index (Cho and Kensey, 1991), diabetes mellitus, arterial hyper- tension, sepsis (Meiselman and Baskurt, 2006), etc. The blood viscosity models in literature may however be dis- cussed in two main categories namely; ***Newtonian viscosity models*** *and* ***non-Newtonian viscosity models***

Newtonian viscosity models

The blood behaves like a Newtonian fluid when shear rate over a limiting value. This apparent limiting viscosity or shear rate is a function of the blood composition, and is primarily modulated by hematocrit (...) blood was modeled as a Newtonian fluid in some studies by accepting the viscosity of blood to be constant and equal to the blood viscosity (...) However, a considerable amount of attempts has been developed for estimating Newtonian visscosity of whole blood as a function of cell concentration - ***concentration dependent Newtonian models*** *(table given) - (...) n later devel- opments, interactions between particles have been included by adding a quadratic terms and the particle shape have been included*

Some of these models were extended to the non-Newtonian mod- els by taking some model parameters as shear dependent variables (Quemada, 1978; Wildemuth and Williams, 1984; Snabre and Mills, 1996) and by using the differential developing effective medium approach (Pal, 2003).

Non-Newtonian viscosity models

The instantaneous shear rate over a cardiac cycle varies from zero to approximately 1000 s-1 in several large arteries (Cho and Kensey, 1991). Therefore, over a cardiac cycle, there are time periods where the blood exhibits shear thinning behavior. In addition to low shear time periods, low shear exists in some regions such as near bifurcations, graft anastomoses, stenoses, and aneurysm

To model the shear thinning properties of blood, a constitutive equation is necessary to define the relationship between viscosity and shear rate. The various non-Newtonian blood models have been used to relate the shear stress and rate of deformation for the blood flow in large arterial vessels. In addition to shear thinning behavior, thixotropic and elastic behaviors of blood have also been taken into account by various researchers. All of these models can be classified into two categories as ***time independent*** *and* ***time dependent flow behavior models***

The constants of the time independent models were obtained by means of parameter fitting on experimental viscosity data obtained at certain shear rates under steady state conditions

Experimental limitations: *At this point it should be noted that; many existing vis- cosity data of whole blood were taken under assumption of Newtonian flow pattern in the rheometers measurement field and ignored slip effect. In addition to these criteria, some data have been fitted and used with neglecting the effect between physiologic blood temperature and medium temperature of measurement on CFD studies. All of these assumptions can cause to errors!(...) Therefore, apparent shear rate and viscosity need to*

corrections. Some correlation methods for blood or Casson fluid like blood have been used in the literature (Janzen et al., 2000; Joye, 2003; Zhang and Kuang, 2000), but they need to include the effect of hematocrit or void fraction. Since different flow patterns may be observed at different hematocrit values.

*The **slip effect** is a common feature for all types of two- phase or multiphase systems like blood (Barnes, 1995). It is significant only if the slip layer is sufficiently thick or the viscosity of the slip layer is sufficiently low (Coussot, 2005). Blood has the low viscosity of the continuous phase, the high concentration of the suspensions, and finally, the relative large size of RBCs and its aggregates compared to usual wall roughness. Therefore, significant amount of slip is to be expected for blood under the appro- priate conditions. Slipping of RBCs in contact with the wall in vivo and in vitro has been observed in literatur (...) As a result of the shear induced migration of blood cells away from wall boundaries, a cell-rich layer surrounded by a cell-deplated plasma layer at the wall occurs. et al., 1992). The interface between these layers is a rough surface due to the presence of the RBCs, and the protrusion of blood cells into the plasma layer may give additional energy dissipation (Sharan and Popel, 2001). Narrow marginal layer of plasma has a lower vis- cosity than the rest of the fluid and serve as a lubricant so that slip occurs. The slip effects and the effects of fibrinogen level and hematocrit on it at low shear rates were studied (Picart et al., 1998a; Picart et al., 1998b) and found that; migrational and slip effects are more pronounced as shear rate decreased, fibrinogen concentration is raised, and hematocrit is lowered. Aggregation behavior of RBCs at low shear rates and increase of the fibrinogen level could give rise to effective particle size, and lower hematocrit could give rise to the slip layer thickness. As a result, the slip effect can cause to experimental errors on viscosity data of whole blood if not eliminate or taken into accoun (**slip effect leads to erros**)*

Another experimental limitation is that the viscosity models are based on experimental data obtaining the result- ing shear stress response to shear rate after an acceptable amount of time has passed to allow rouleaux formation, although the time between consecutive strokes is not suf- ficiently long for the segregated RBC to reaggregate

Time independent viscosity models

show shear thinning behavior and must meet the following model requirements: There are three distinct regions for apparent blood viscosity:

1. *lower Newtonian region (low shear rate constant viscosity, μ_0)*
2. *an upper Newtonian region (high shear rate constant viscosity, μ_∞),*
3. *and a middle region where the apparent viscosity is decreasing with increasing shear rate, $\frac{\partial \mu}{\partial \gamma} < 0$*

***Power law equation** is a suitable model for the middle region. However, it does not describe the low and high shear rate regions*
***Herschel-Bulkley model** extends the power law model to include the yield stress, τ_γ*
The other models which include yield stress are also shown in Table 3

The models that have limitation at low and high shear rates can easily figure out when shear rate in models are taken as zero or infinity (whole table with all the models zero or infinity. Casson, Walburn-Schneck, and Weaver models include the effect of the RBC concentration, Walburn-Schneck model also incorporates fibrinogen and globulins proteins, TPMA. A log-log plot of the apparent blood viscosity as a function of shear rate can be also used to figure out how much is closely matched each model and model parameters with healthy experimental blood vis- cosity data.

The study on 11 viscosity models of Easthope and Brooks (1980) concluded that the Walburn and Schneck model is in well agreement in the shear rate range of 0.03-120 s-1. Sugiura (1988) showed that viscosity model in that shear rate should be Weaver model ... different results

TABLE WITH MANY TIME INDEPENDENT MODELS

Time dependent viscosity models

Time-dependent models are used to describe thixotropic and viscoelastic behavior. Thixotropy is a special condition of pseudo plasticity with or without yield stress, where the apparent viscosity also decreases when the fluid is subjected to a constant shear rate. Blood is a concentrated sus- pension of cells. Most of concentrated suspension system exhibits thixotropic behavior. Experimental results of whole human blood have demonstrated that blood is a exhibits thixotropic behavior. ...the hematocrit, gender and age are factors affecting the blood thixotropy

Chen et al., 1 991; Huang et al., 1987b). Huang developed a generalized rheological equation for thixotropic fluids. Huang model parameters were calculated from experimental data by non-linear parameter estimation technique for apparently healthy human subjects

TABLE WITH 4 TIME-DEPENDENT THIXOTROPIC MODELS
Huang model, Weltman Model, Tiu-Boger Model, Rosen Model

In literature, viscous models obtained at steady state con- ditions were used under pulsatile flow conditions. These models have provided a great deal of insight into the non- Newtonian viscous behavior of blood. However, blood exhibits both viscous and elastic properties under pulsatile flow

Viscosity is an assessment of the rate of energy dissipation due to cell deformation and sliding, while elasticity is an assessment of the elastic storage of energy primarily due to kinetic deformability of the RBCs

There are two dimensionless numbers to measure of the tendency of a material to appear either viscous or elastic; the Deb-orah number and the Weissenberg number. The Deborah number is the ratio of the relaxation time to the characteristic time of the flow $De = \Theta_r/T_c$*, with The relaxation time can be defined as a ratio of the viscosity to elatisity* $\Theta_r = \mu/G$*. Three ranges of Deborah number are identified as that; if* $De << 1$ *, the material is viscous, if* $De \approx 1$ *, the material will act viscoelastically, and if* $De >> 1$*, the material is elastic (Steffe, 1996).*

The Weissenberg number is defined as the ratio of the characteristic time of fluid to a characteristic convective time-scale of the flow or the characteristic shear rate times the relaxation time $We = \Theta_r\dot{\gamma}_c$

Blood is slightly viscoelastic, and its effect was ignored in most of the CFD studies. At low shear rates, RBCs aggregate are solid-like bodies, and has ability to store elastic energy. Its value remains constant for shear rates up to 1 s-1 (Thurston, 1979). At high shear rates, its effect is less prominent because the RBCs behave fluid-like bodies (Schmid-Schoenbein and Wells, 1969), and lose this ability (Anand and Rajagopal, 2004). Viscoelastic models can be suitable for blood flow under certain flow conditions especially at low shear stress. It also grows in importance when flow is oscillatory (Rojas,

The extra stress tensor is used to characterize the viscoelastic stress in viscoelastic models. The total stress tensor (Cauchy stress tensor) is defined in terms of the pressure (P) and the extra stress tensor (S). $\boldsymbol{\sigma} = -P\boldsymbol{I} + \boldsymbol{S}$

Different models for capturing viscoelastic properties of blood:

1. **Oldroyd-B Model**
2. **Yeleswarapu Model**
3. **Generalized Oldroyd-B Model** (Rajagopal and Srin- ivasa, 2000)
4. **Generalized Maxwell Model** (Rajagopal and Srin- ivasa, 2000)
5. **Generalized Oldroyd-B Model** (Anand and Rajago- pal, 2004) *All of the Rajagopal models have a thermodynamic basis and generalized Oldroyd-B models of Rajogopal are not capable of an instantaneous elastic response*
6. **Generalized Maxwell Model** (Owens, 2006)

Yield stress of blood

The yield stress of blood can be taken into account in the regions of low shear rates like thixotropic and viscoelastic behavior of blood. It can supply better understanding of aggregation and deformation of blood cells. The relation of cell deformation and aggregation with yield stress was described as

Formulas for yield stress

Accurately and functionally representing of blood behav- iors in the viscosity models and the local hemodynamic environment are very important and increases performance of a CFD model. Therefore, there is a need for a viscosity model based on the internal structures of blood. Addi- tionally, there are some cautions in the evaluation of accu- rate experimental data for blood constitutive parameters. The local environment strongly impacts the local flow pat- terns and hence shear rate. Expressing of accurate envi- ronment is therefore possibly essential. However, assump- tions on the physiological conditions are mandatory

Physiological conditons

The cyclic nature of the heart pump creates pulsatile con- ditions in arteries, and therefore blood flow and pressure are unsteady. The pulsations of flow are damped in the small vessels, and the flow is so effectively steady in the capillaries and the veins. The arteries are not rigid tubes. It adapts to varying flow and pressure conditions by enlarg- ing or shrinking. All of these physiologic conditions and others cause difficulties to render simulations both con- ceptually and computationally tractable. As a result, most CFD models of arterial hemodynamics need to make the simplifying assumptions of rigid walls, steady flow, fully developed inlet velocities, Newtonian rheology, normal and periodic flow conditions, ignoring of small side or ter- minal branches, using of idealized or averaged artery mod- els, and using of in vitro experiments to validate CFD models (Steinman, 2002; Steinman, 2004; Steinman and Taylor, 2005)

Conclusion

Although there has been the considerable amount of viscosity models in blood rheology, none of them has been commonly agreed upon or used. None of the models is fully expressing the effects of extremely complicated nature of blood rheology and its depen- dence of many factors. The groovy method used for

obtaining the existing viscosity models is the para- metric curve fitting on experimental apparent viscosity versus shear rate data, although the blood con- stitutive parameters in these models have been found to be related to internal structures of the blood such as RBC aggregation, RBC deformability, etc. The dependency of blood viscosity on each rheological property of the blood should be investigated and clar- ified separately by means of isolating the effects of remaining rheological properties.

The re-aggregation and viscoelastic behavior of blood detected in realistic pulsatile flows are much different from the corresponding behavior in steady flow. The blood viscosity models fitted on the data measured in the rheometer under the steady flow conditions are so not suitable for the analysis of realistic pulsatile blood flow. Observed blood apparent viscosity in the rhe- ometers under the assumption of Newtonian flow pat- tern is also not suitable and the hematocrit value of tested blood also affects this pattern. The assumption of Newtonian pattern and neglecting the hematocrit effect on it can cause errors. The slip effect in the rhe- ometers should also be prevented throughout the mea- surements.

Thixotropy must be considered in the regions of a substantial RBC residual time to allow the separated RBC to re-aggregate such as aneurysms and recir- culation zones

Viscoelasticity and thixotropy have generally accept- ed as less important for high shear regions. Even so, there is more need to develop in this area for low shear regions. Recent increases in study on viscoelastic models and its application in literature may be an evidence of this.

2.6 Advanced constitutive modeling of the thixotropic elasto-visco-plastic behavior of blood: Description of the model and rheological predictions

Blood is a complex suspension of red blood cells (RBCs), white blood cells (WBCs) and platelets in an aqueous solution, the so-called plasma, containing dissolved proteins [1]. Although many works consider blood as a Newtonian fluid [2,3], in fact, it has a pronounced non-Newtonian character, mostly explained in terms of the ability of RBCs to aggregate/disaggregate, deform and align to flow.

*At **low shear rates**, blood proteins enhance the formation of a complicated network made up of column-like red cell aggregates known as rouleaux, while at almost stasis, the rouleaux forms three-dimensional networks*

*At **higher shear rates**, these structures tend to disintegrate, leading to a state where the red blood cells flow separately*

The physical mechanism that drives the creation of rouleaux is not settled yet but two theories emerge as potential candidates, namely the bridging of fibrinogen [9,10] and the depletion theory. [...] The aforementioned behavior necessitates the use of sophisticated rheological models to capture adequately the rheological response of blood.

*An indicative example is the coagulation process, which initiates the formation of a fibrin network along with the clumping of red blood cells giving rise to enhanced **elastic aspects**. The latter process becomes of significant importance when clotting of blood occurs [22,23], and the influence upon tissue is much more severe than when only the blood viscosity, which is another significant hemorheological parameter, is increased. It should be mentioned that during the clotting process, the elastic modulus varies with time by many orders of magnitude especially for a diabetic blood*

Based on our previous discussion, it is perceivable that the rheological characterization of blood can be divided in two categories: steady state analysis and transient analysis

***Blood possesses a distinct property according to which it flows as fluid if subjected to large enough stresses but behaves as a soft matter if the applied stress is below a critical value, giving rise to the experimentally measured blood yield stress [25,26]. The latter is an essential component of its non-Newtonian nature, stemming explicitly from the creation of rouleaux.** Its role is most clearly evaluated under steady-state shear flow conditions*

Additionally, the well-known shear thinning behavior of blood has been described by a plethora of investigations [30,31] in various hemodynamical conditions as well as the existence of a critical hematocrit associated with blood yield stress and the transition from non-Newtonian to Newtonian flow in high shear rates

However, blood possesses also a non-negligible elastic nature, as shown experimentally [33,34]. Apparently, this is an inherent property of blood, [35,36] and it can be associated with the lipidic bilayer membrane of RBCs and hemorheological variables such as hematocrit and fibrinogen concentration

Blood is also classified as a non-ideal yield-stress material due to its non-negligible elastic effect. Thus, the need to introduce the concept of elasto-visco-plastic (EVP) fluids is clear to describe materials that have elastic and plastic characteristics simultaneously.

Although the findings of the aforementioned investigations are important, the inherent properties of blood are strongly time-dependent as well, and thus, blood is categorized as a thixotropic material. From a

rheological perspective, blood is one of the most characteristic examples of a thixotropic fluiand allows for the evaluation of generalized thixotropy models for a unique and biologically relevant case. ***A thixotropic fluid is a fluid whose material properties (e.g., viscosity) is a function not only of the applied stress but also of the previous history of motion within the fluid [5,21,24,40,41]. The thixotropic nature of blood stems from the aggregation/disaggregation of rouleaux which is governed by its own time scales affected by the concentration of plasma proteins [42] and hematocrit***

Transient blood flow phenomena: ***In particular, the yield stress in dense, soft colloidal suspensions such as blood is typically attributed to an internal structure that develops, deforms, and decays in a way that depends critically not only on the current flow kinematics but also on its deformation history, thus giving rise to thixotropy***

The rheological modeling of blood should consider all the above phenomena to predict a realistic behavior. Therefore, the focus has been shifting towards constitutive equations that incorporate plasticity, elasticity and thixotropy.

The model of Owens and coworkers [...] lacks explicit accounting for yield stress, the most important manifestation of the viscoplastic nature of blood

dditionally, Anand and Rajagopal [55] used a generalized Oldroyd-B model, which was developed in the context of the general thermodynamic framework of Rajagopal and Srinivasa [56]. They made use of a tensorial viscoelastic model and therefore do not explicitly take into account the viscoplastic nature of blood, although their work was found to agree with steady-state and transient experiments

....

2.7 An Overview of Some Mathematical Models of Blood Rheology

Experimental investigations over many years reveal that blood flow exhib- its non-Newtonian characteristics such as shear-thinning, viscoelasticity and thixotropic behaviour. The complex rheology of blood is influenced by nu- merous factors including plasma viscosity, rate of shear, hematocrit, level of erythrocytes aggregation and deformability.

Blood is a multi-component mixture with complex rheologic characteristics which interacts both mechanically and chemically with vessel walls, giving rise to complex fluid-structure in- teraction models whose mathematical analysis is still incomplete and which are difficult to simulate numerically in an efficient manner. The

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 de- velopment of arterial diseases. (...) 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 ves- sels. The combined effects of complex arterial geometry with flow pulsatility and rheology induce low oscillating wall shear stress, high pressure distri- bution and a enhanced particle residence time in flow separation and flow recirculation zones, resulting in a locally distributed mass transfer

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 ab- dominal 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

Clinically relevant hemodynamic parameters, including pressure, velo- city, blood flow patterns and shear stress, can be directly or indirectly quanti- fied. Experimental

Blood is a suspension of cellular deformable components (red blood cells,Â¸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 of- ten 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 con- stant 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 (capil- laries) 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

BLOOD MORPHOLOGY AND VISCOMETRIC PROPERTIES

Blood is a multi-component mixture with complex rheological character- istics. It consists of multiple cellular elements:

1. ***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*
2. ***white blood cells*** *- WBCs (leukocytes) are much less numerous than RBCs, they have nuclei, and are classified into two groups - are involved in the organisms defence against invasion by bacteria and viruses - Rather little is known of the mech- anical 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*
3. ***platelets (thrombocytes)****, small discoid cell fragments containing various chemicals such as serotonin, thrombin, ADP, are much smaller than erytrocytes - they have a negligible effect on the mechanics of normal blood, compared to erythrocytes.*
4. ***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*

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 (..) 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.

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 prop- erties 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.

Deformability and rotation of membran: *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 ofmaximum thickness) and filled with a saturated solution of hemoglobin, which are cap- able of extreme distortion, without changing their surface area, as when they travel along capillaries with diameters smaller than their own.Another phe- nomenon 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]).*

Rouleaux and network formation: *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 addi- tional increase of the*

viscosity. The time required for building a network is even longer than for rouleaux formation. This mechanism is still incom- pletely understood. It appears that the erythrocytes attract one another and the process depends in particular on the influence of bridging macromolec- ules, especially fibrinogen and globulins in the plasma. ***The process will not occur in their absence and it occurs progressively faster with increas- ing concentration of these macromolecules***

Higher shear rates: *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 Fahraeus-Lindqvist effect [20] (cell aligne- ment and plasma skimming), Fahraeus effect [19] (dymanic reduction of hematocrit in small vessels) and sedimentation, reducing the apparent vis- cosity of blood in the microvessels

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 memor 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 in- dividual cells, that are characterized by distinct relaxation times. RBCs be- come 'fluid-like', losing their ability to store elastic energy and the dissip- ation is primarily due to the internal frictiony

Viscoelastic: *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****.*

Thixotropy: *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*

The rheological behaviour of blood is mainly governed by the concen- tration 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 in- terpreted with caution.

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 deformab-ility 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.

Blood platelets participate in both hemostasis and thrombosis by adhering to damaged vessels and by getting activated releasing chemic- als (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 aggreg- ate interacts with fibrin to form irreversible hemostatic plugs

Numerous clinical and experimental studies recognized that thrombus form- ation occurs not in regions of parallel flow, but primarly in regions of stagna- tion point flows, within blood vessel bifurcations, branching and curvatures. Moreover, internal cardiovascular devices such as prosthetic heart valves, ...

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 chem- ical and cellular transport ...

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.

BLOOD CONSTITUTIVE MODELING

In large and medium sized vessels blood can be modelled as an homogen-eous 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 read in general form

$$\frac{\partial \boldsymbol{u}}{\partial t} + \rho(\boldsymbol{u} \cdot \boldsymbol{\nabla})\boldsymbol{u} = \boldsymbol{div}(\boldsymbol{\sigma}) + \boldsymbol{f} \tag{33}$$

$$\boldsymbol{div}(\boldsymbol{u}) = 0 \tag{34}$$

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

$$\boldsymbol{\sigma} = -p\boldsymbol{I} + 2\eta\boldsymbol{D} \tag{35}$$

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

$$\boldsymbol{D} = \frac{1}{2}(\nabla\boldsymbol{u} + (\nabla\boldsymbol{u})^T) \tag{36}$$

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 inlet and outlet surface . 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) formula- tion 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*)

blood is essentially a non-Newtonian fluid and the constitutive equations for blood must incorporate the non-linear viscometric properties of blood previously discussed. (..) 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 New- tonian or inelastic models and viscoelastic models

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, mean- ing 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*

$$\boldsymbol{\sigma} = \phi_0 \boldsymbol{I} + \phi_1 \boldsymbol{D} + \phi_2 \boldsymbol{D}^2 \tag{37}$$

and ϕ_{0-2} 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 $III_D = det(\boldsymbol{D})$

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

$$\boldsymbol{\sigma} = \alpha \boldsymbol{I} + \phi_1 \boldsymbol{D} + \phi_2 \boldsymbol{D}^2 \tag{38}$$

where α *is a Lagrange multiplier connected to the incompressibility con- straint and* $\phi_{1,2}$ *only depend on* II_D, III_D *:* ***These fluids are generally known has Reiner-Rivlin fluids***

Finally, if we consider that the dependence of ϕ_1 *on* III_D *is negligible, we obtain the so called* ***Generalized Newtonian fluid;*** *Thermodynamic considerations and the analysis of their behaviour under simple shear (and other viscometric flows) leed to the final form of* $\boldsymbol{sigma}$

$$\boldsymbol{\sigma} = -p\boldsymbol{I} + 2\eta(\dot{\gamma})\boldsymbol{D} \tag{39}$$

where $\dot{\gamma} = \sqrt{2\boldsymbol{D} : \boldsymbol{D}}$ *ist 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 provided (poewr law, powell-eyring, cross, modified cross, carreau, carreau-yasuda)

Attempts to recognize the shear-thinning nature of blood were initiated by Chien et al. in the 1960s. Empirical models like the power-law (or Walburn-Schneck power-law, 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 vis- cosity 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 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 ***Cassons 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 ho- mogeneized models are capable of describing the viscoelastic response of blood*

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*

$$\boldsymbol{S} + \lambda_1 \overset{\triangledown}{\boldsymbol{S}} = 2\mu_0 \boldsymbol{D}, \quad \boldsymbol{\sigma} = -p\boldsymbol{I} + \boldsymbol{S} \tag{40}$$

where $\boldsymbol{S}$ *is the extra-stress tensor and the upper traiangle stands for the upper-convected de- rivative of a tensor field*

$$\overset{\triangledown}{\boldsymbol{S}} = \frac{\partial \boldsymbol{S}}{\partial t} + (\boldsymbol{u}\cdot\nabla)\boldsymbol{S} - \boldsymbol{S}\cdot\nabla\boldsymbol{u} - (\nabla\boldsymbol{u})^T\cdot\boldsymbol{S} \tag{41}$$

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 mod-els****, can be defined by*

$$\boldsymbol{S} + \lambda_1 \overset{\triangledown}{\boldsymbol{S}} = 2\mu_0(\boldsymbol{D} + \lambda_2 \overset{\triangledown}{\boldsymbol{D}}) \tag{42}$$

where λ_2 *is the relaxation time, with* $0 \le \lambda_2 < \lambda_1$

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* $\boldsymbol{S} = \boldsymbol{S}_1 + \boldsymbol{S}_2$*. The corresponding stress relations become*

$$\boldsymbol{S}_1 + \lambda_1 \overset{\triangledown}{\boldsymbol{S}_1} = 2\mu_1 \boldsymbol{D}, \tag{43}$$

$$\boldsymbol{S}_2 = 2\mu_2 \boldsymbol{D}, \tag{44}$$

(also see Hemorheology: Non-Newtonian Constitutive Models for Blood Flow Simulations (in Non-Newtonian Fluid Mechanics and Complex Flows: Levico Terme, Italy 2016)) where μ_1 *is the elastic viscos ity and* μ_2 *the Newtonian viscosity. It can be shown that*

$$\mu_0 = \mu_1 + \mu_2 \quad \textit{and} \quad \lambda_2 = \mu_2\lambda_1/\mu_0 \tag{45}$$

If $\lambda_2 = 0$ *the model reduces to the upper-convected Maxwell fluid (8), while if* $\lambda_{1,2} = 0$ *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 .... 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 as-sociated 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

Other viscoelastic models and their results *As already referred in Section 2.1 various attempts have been made to re- cognize 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 describ- ing 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 ob- servations****. 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 relaxa- tion times depending on the shear rate and gives good agreement with exper- imental 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].*

SOME NUMERICAL SIMULATIONS

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 lay- ers 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

Geometric reconstruction and mesh generation *The most common medical imaging technique presently used to obtain 3D representations of the human body is magnetic resonance (MR)...The challenge is not to collect the data but to be able to translate them into something usable in computer simulations.*

Interesting but yet not important for me

Finite element method and results *In the case of Newtonian or generalized Newtonian fluids the extra-stress tensor 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)*

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***

The Carreau-Yasuda velocity shows a flattened profile (larger region of higher velocity), reaching a lower maximum value

Hemorheology: Non-Newtonian Constitutive Models for Blood Flow Simulations

Experimental studies over many years have shown that blood flow exhibits non-Newtonian characteristics such as shear-thinning, viscoelasticity, yield stress and thixotropy.

The complex rheology of blood is influenced by numerous factors including plasma viscosity, hematocrit and in particular, the ability of erythrocytes to form aggregates when at rest or at low shear rates and to deform at high shear rates, storing and releasing energy

Blood Rheology

Blood components Detailed decription with numbers of the single components

Non-Newtonian Properties of Blood *The non-Newtonian behavior of blood is largely due to three characteristics of RBCs: their ability to formaggregates when at rest or at low shear rates, their general distribution in the flowing plasma, namely the ability of these 3D microstructures to deform and store energy and their tendency to align in the flow direction, at high shear rates (e.g. [29, 111]). The high deformability of RBCs is due to the absence of a nucleus, to the elastic and viscous properties of its membrane and also to geometric factors such as the shape, volume and membrane surface area [27]*

As discussed below, it has been experimentally verified that the response ofRBCs in shear flows undergoes three flow regimes: at low shear rates, in the presence of fibrinogen and large globulins (proteins found in plasma) erythrocytes form a complex three dimensional microstructure (rouleaux), while at high shear rates, this microstructure is lost and flow induced radial migration may lead to a non- homogeneous distribution of erythrocytes. A transition in microstructure is found between these two regimes

Viscosity of Blood *Here we refer to the apparent viscosity of blood (or, more generally of a non-Newtonian fluid, independently of the specific rheological model) (..) This is approximately an average measure of the fluid resistance to flow. The expression relative viscosity is also used for blood, denoting the ratio of the suspension viscosity (apparent viscosity) to the viscosity of the suspending fluid (plasma).*

Usually blood has higher viscosity than plasma, and when the hematocrit rises, the viscosity of the suspension increases and the non-Newtonian behavior of blood becomes more relevant, in particular at very low shear rates. As mentioned above, for blood at rest or at very low shear rates the erythrocytes have the ability to form a primary aggregate structure of rod shaped stacks of individual cells (rouleaux), that align to each other and form a secondary structure consisting of branched three-dimensional (3D) aggregates [112]. The apparent viscosity (measured by a viscometer) increases slowly until a shear rate less than 1 s-1, and then it increases significantly [24]. It has been experimentally observed that rouleaux will not form if the erythrocytes have been hardened or in the absence of fibrinogen and globulins. ... (For standing blood subjected to a shear stress lower than a critical value, these 3D structures resist to flow until a certain force is applied and blood exhibits a yield stress behavior. This can happen only if the hematocrit is high enough. The existence of yield stress for blood will be discussed below (see Sect. 2.2.2))

At moderate to high shear rates, RBCs are dispersed in the plasma and the properties of the blood are influenced by their tendency to align and form layers in the flow, as well as by their deformation. The effect of RBC deformability on the viscosity of suspensions was clearly described in [28].

For shear rates above 400 s-1, erythrocytes lose their biconcave shape, become fully elongated and are

transformed into ellipsoids with major axes parallel to the flow direction. The tumbling of the erythrocytes is absent, there are almost no collisions, and their contours change according to the tank-trading motion of the cells membranes about their interior. The apparent viscosity decreases and this becomes more evident in smaller than in larger vessels. This happens with vessels of internal diameter less than 1mm and it is even more pronounced in vessels with a diameter of 100-200μm. The geometric packing effects and radial migration of erythrocytes can act to lower the hematocrit adjacent to the vessel wall and contribute to decrease the blood viscosity. This is known as the Fahraeus-Lindqist effect, [41, 42]. Plasma skimming is another effect that results in diminishing the viscosity when blood flows into small lateral vessels compared with the parent vessel.

As a consequence of this behavior we can say that one of the most important non- Newtonian characteristics of blood is the shear-thinning viscosity. This happens in small size vessels or in regions of stable recirculation, like in the venous system and parts of the arterial vasculature where geometry has been altered and erythrocyte aggregates become more stable, like downstream a stenosis or inside a saccular aneurysm. However, in most parts of the arterial system, blood flow is Newtonian in normal physiological conditions.

(...) the temperature at which data was obtained must be considered. The dependence of blood viscosity on temperature is similar to that of water for temperatures (...)!

Yield Stress of Blood *This critical stress level, called the yield value or yield, is typically treated as a constant material property of the fluid. An extensive description of methods for measuring yield stress is given in [89, 92].*

Rather than treating the yield stress as a constant, it should be considered as a function of time and linked to thixotropy, as later proposed by other researchers [88]. Some studies have indicated that yield stress is correlated to the hematocrit level and to the concentration of fibrinogen in blood plasma. When the hematocrit level falls below a critical level, the yield stress characteristic of blood becomes negligible [83]

Viscoelasticity and Thixotropy of Blood Viscoelastic *Viscoelastic fluids are viscous fluids which have the ability to store and release energy. The viscoelasticity of blood at normal hematocrits is primarily attributed to the reversible deformation of the RBCs 3Dmicrostructures [30, 128]. Elastic energy is due to the properties of the RBC membrane which exhibits stress relaxation [36, 119] and the bridging mechanisms within the 3D structure. Moreover, the experimental results of Thurston [124] have shown that the relaxation time depends on the shear rate. Thurston was the first to measure the viscoelastic properties of blood and the dependence of blood viscoelasticity on factors such as temperature, hematocrit and RBC properties. He has contributed to most of the experimental work developed in this area (see [128] and the references cited therein). The viscoelastic effects in blood circulation are magnified by its pulsatile nature and by the elastic properties of the blood vessels and the porous tissue through which blood is transported [23] and there is an interaction between the viscoelastic behavior of blood with that of the vessel wall and porous tissue*

By shear rates of the order of 10 s-1 the elastic nature of blood is negligible as evidenced by a merging of the oscillatory and steady flow viscosities. However, if viscoelastic constitutive equations are used to model blood in the circulatory system in higher shear rates conditions, the finite viscoelastic behavior of blood should be considered

Another important non-Newtonian property of blood closely related to shear-thinning, is the thixotropic behavior, essentially due to the finite time required for the formation and dissolution of the 3D aggregates

of erythrocytes. Indeed, the build-up and breakdown of the 3D microstructures, their elongation and recovery, and the formation and breakdown of layers of the aligned erythrocytes evolve in a finite time, and these processes can play an important role in blood rheometry

When a reduction in magnitude of rheological properties of a system, such as elastic modulus, yield stress, and viscosity, for example, occurs reversibly and isothermally with a distinct time dependence on application of shear strain, the system is described as thixotropic

Thixotropy is more pronounced at low shear rates with a long time scale. The effect in blood flow is less pronounced than other non-Newtonian effects [78]and this can explain the limited studies devoted to this property

Constitutive Models for Blood

The mechanical properties of blood should be studied by considering a fluid containing a suspension of particles. A fluid is said to be Newtonian if it satisfies the Newtons law of viscosity (the shear stress is proportional to the rate of shear and the viscosity is the constant of proportionality). Blood plasma, which consists mostly of water, is a Newtonian fluid. However, the whole blood has complex mechanical properties which become particularly significant when the particles size is much larger, or at least comparable, with the lumen size. In this case, which happens at the microcirculation level (in the small arterioles and capillaries) blood cannot be modelled has a homogeneous fluid and it is essential to consider it as a suspension of blood cells (specially erythrocytes) in plasma.

Blood is a non-Newtonian fluid, but it can however be regarded as Newtonian depending on the size of the blood vessels and the flow behavior, as in arteries with diameters larger than 100 μm where measurements of the apparent viscosity show that it ranges from 0.003 to 0.004 Pa s and the typical Reynolds number is about

Here we assume that all macroscopic length and time scales are sufficiently large compared to length and time scales at the level of an individual erythrocyte so that the continuum hypothesis holds.

Constant Viscosity Models NAVIER-STOKES-EQUATION

When $Re << 1$ (for instance blood flow in smaller arteries), we may neglect the convective term compared to the viscous contribution. Then blood could be modeled by the simpler Stokes equations (creeping flow or Stokes flow). However, as already mentioned, in the smaller arteries the non-Newtonian behavior of blood the flow becomes unstable. In normal physiological conditions instabilities can becomes relevant. On the other hand, when $Re >> 1$(high Reynolds number flows) occur in some vascular regions, in particular in the systolic phase at the exit of the aortic valve or in bifurcations, but normally there is no time for the flow to develop turbulence. In pathological conditions, like in case of severe anaemia (low blood viscosity) or due to the presence of a stenosis (stenotic artery), the transition from laminar to turbulent flow can occur [44]. Such conditions are nevertheless rare and consequently turbulent flow models are not used in cardiovascular modeling and simulations.

Generalized Newtonian Models *As already discussed, this set of equations is commonly used to describe blood flow in healthy arteries. However, under certain experimental or physiological conditions, particularly at low shear rates, blood exhibits relevant non-Newtonian characteristics and more complex constitutive models need to be used. In this case, we require a more general constitutive equation relating*

the state of stress to the rate of deformation

Reiner Rivlin - Genrealized Newtonian - Power law *One of the important extensions of the power-law model is due to Walburn and Schneck [133] who considered the dependence of the viscosity on the hematocrit (Ht) and total protein minus albumin (TPMA) in the constants n and K, based on nonlinear regression analysis, and found*

very similar to other paper

Yiel stress Casson Model and Quemanda

Viscoelastic *There is a large number of in vitro experiments confirming that blood can store and dissipate energy during the aggregation of the erythrocytes and the distortion of the formed 3D microstructures (e.g. [30, 77, 125, 131]. As previously mentioned in Sect. 2.2.3, Thurston [124] was among the earliest to recognise the viscoelastic nature of blood and that the viscoelastic behaviour is less prominent with increasing shear rate. In view of the available experimental evidence, it is reasonable to develop non-Newtonian fluid models for blood that are capable of shear-thinning and stress*

the so-called upper-convected derivative (...) is a generalization of the material time derivative. (...) is chosen to be objective under a superposed rigid body motion, meaning that it is frame indifferent or that the response of the material is not affected by its location and orientation. The resulting second-order tensor is symmetric

Oldroyd type models: *The Oldroyd type fluids can be considered as Maxwell fluids with additional viscosity.*

In order to better understand the theory of viscoelasticity it is useful to illustrate the typical behavior of viscoelastic materials by simple mechanical models, where a dashpot (piston moving inside a cylinder filled with liquid) represents a viscous (Newtonian) fluid and a spring stands for an elastic (Hookean) solid. These elements can be connected in series or in parallel and the analysis of the behavior of different viscoelastic materials can be done through their combinations representing various deformation-stress model

This is the constitutive equation for the viscoelastic isothermal Oldroyd-B fluid. The governing equations for the Oldroyd-B fluid are obtained by considering the basic principles of conservation of linear momentum and mass for isothermal incompressible flows, where the extra stress is decomposed as in (24), the Newtonian part being represented by (25) and the viscoelastic component satisfying the constitutive equation (31).

The Oldroyd-B model accounts for the viscoelasticity of blood but not for its shear-thinning behavior. However, replacing the constant viscosity of the solvent by a shear dependent viscosity function using, for instance one of the generalized Newtonian models listed in Table 3 with the corresponding parameters, we obtain a generalized Oldroyd-B (GOB) model that can be appropriate to describe blood flow behavior. Other viscoelastic constitutive models of differential type, suitable to account for blood rheology have been proposed in the recent literature. The empirical five- constant generalized Oldroyd-B model studied in [132] belongs to this class. It is a shear-thinning Oldroyd-B model with the shear-dependent viscosity ...

3 Derivation of Navier-Stokes Equation

3.1 Cardiovascular mathematics Chapter 3

Momentum equation

The conservation of (linear) momentum is in fact the well known ***Newtons law****. The rate of change of the momentum of a material domain $V(t)$, given by $\int_{V(t)} \rho \mathbf{u} \mathbf{dx}$ equals the resultant of the external forces acting on it, that is*

$$\frac{d}{dt}\int_{V(t)} \rho \mathbf{u} \mathbf{dx} = \mathbf{F} = \mathbf{F_v} + \mathbf{F_s} \tag{46}$$

The force F is the composition of two terms: ***a volume force*** *F_v****,and a surface force*** *F_s. The former acts on each particle of V(t) (like the force of gravity) and is expressed as the integral of the density times a specific force (i.e. force per unit of weight) f which has the dimension of an acceleration,*

The surface force is instead responsible for the mutual interaction between the material contained in V(t) and the exterior, through the boundary $\partial V(t)$. More precisely, F_s is equal to the surface integral of the so called Cauchy stress $\boldsymbol{T}(\boldsymbol{x}, t, \boldsymbol{n})$, which has the dimension of force per unit area, [t]= N/m^2,that is

$$F_s = \int_{\partial V(t)} \boldsymbol{T} d\gamma \tag{47}$$

It was indeed Cauchy who also postulated that $\boldsymbol{T}$ can be computed by applying to the normal $\boldsymbol{n}$ of $\partial V(t)$ a symmetric second-order tensor

$$\boldsymbol{\sigma} : \Omega(t) \longrightarrow \mathrm{R}^{3x3} \tag{48}$$

called the ***Cauchy stress tensor*** *$\boldsymbol{\sigma}(\boldsymbol{x}, t)$, i.e.*

$$\boldsymbol{T} = \boldsymbol{\sigma n} \ on \ \partial V(t) \tag{49}$$

The momentum conservation law can then be expressed by the following equation

$$\frac{d}{dt}\int_{V(t)} \rho \mathbf{u} \mathbf{dx} = \int_{\mathbf{V(t)}} \rho \mathbf{f} \mathbf{dx} + \int_{\mathbf{V(t)}} \mathbf{div} \sigma \mathbf{dx} \tag{50}$$

To obtain the last equality we have used the divergence theorem. Finally, by exploiting the Reynolds transport formula:
Let $V(t)$ be a material domain, i.e. $V(t) = \boldsymbol{x} : \boldsymbol{x} = \tilde{\boldsymbol{\phi}}(\tilde{\boldsymbol{x}}, t), \ \tilde{\boldsymbol{x}} \in \tilde{\boldsymbol{V}}$,and f a continuously differentiable field, Then

$$\frac{d}{dt}\int_{V(t)} f \, d\boldsymbol{x} = \int_{V(t)} (\frac{\partial f}{\partial t} + div(f\boldsymbol{u}))\, d\boldsymbol{x} \tag{51}$$

So finally we obtain: Momentum conservation in quasi-linear form

$$\rho \frac{\partial \boldsymbol{u}}{\partial t} + \rho(\boldsymbol{u} \cdot \nabla)\boldsymbol{u} = div\boldsymbol{\sigma} + \rho \boldsymbol{f}, \ in \ \Omega(t), \ t > 0 \tag{52}$$

and in conservation form

$$\frac{\rho\partial \boldsymbol{u}}{\partial t} + div(\rho \boldsymbol{u} \times \boldsymbol{u} - \boldsymbol{\sigma}) = \rho \boldsymbol{f}, \ in \ \Omega(t), \ t > 0 \tag{53}$$

The transport term $(\boldsymbol{u} \cdot \nabla)\boldsymbol{u}$ *is a nonlinear term and rises the complexity to solve equation*

At each point of the boundary of a material domain V(t) the Cauchy stress $\boldsymbol{T}$ *can be decomposed into its components normal and tangential to the surface, given respectively by*

$$T_n = \boldsymbol{T} \cdot \boldsymbol{n} = (\boldsymbol{\sigma n}) \cdot \boldsymbol{n}, \quad \boldsymbol{T}_t = \boldsymbol{T} - T_n \boldsymbol{n} \tag{54}$$

The latter is indeed a vector laying on the tangential plane and is called the **shear stress vector. It is an important parameter in haemodynamics since the endothelium cells are very sensitive to the shear stress at the vessel walls. The equations have been here written in Eulerian formulation**

Fluids and Solids - Definition of Cauchy stress tensor!

We need now to make precise how the Cauchy stress tensor is linked to the kinematics. It is indeed at this point where the behaviour of solids and fluids diverges- As solids react to deformations, the Cauchy stress must depend on the deformation gradient $\tilde{\boldsymbol{F}}$*. Fluids instead can adapt to a deformation, as a fluid can fill freely any arbitrary shape. Yet it takes time to fill it. And oil takes more time than water. It means that fluids react mechanically not to the deformation itself but to its rate. More precisely, the relevant quantity is here the strain rate tensor* $\boldsymbol{D}$ *defined in (2.2) of Chapter 2, and whose dimensions are [*$\boldsymbol{D}$ *]=* s^{-1}*. Componentwise, the strain rate reads*(Chapter 3)

$$D_{ij} = \frac{1}{2}(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}) \quad i, j = 1, ...3 \tag{55}$$

As in one of the videos the strain rate tensor corrsponds to the symmetric part of velocity gradient tensor ***In a fluid then the cauchy stress tensor is a function of D, while it is independent of deformation gradient F. A consequence is that the reference configuration is a concept useful for the derivation of the equations, yet it does not play any particular role for a fluid. Intermediate behaviours, like that of visco-elastic fluids, for instance, are possible; they will be addressed in detail in Chapter 6.*** *The relation between the Cauchy stress tensor* $\boldsymbol{\sigma}$ *and the kinematic quantities is called constitutive relation, or constitutive law, and is a characteristic of the type of material under consideration. To be physically correct, a constitutive relation must obey certain rules, like the principle of material frame indifference [512] which states that the relation should be invariant under a change of frame of reference.*(Chapter 3)

Newtonian and Non-Newtonian

In a Newtonian incompressible fluid (this is a limitation usually accepted for blood flow in large arteries), the Cauchy stress tensor depends linearly on the strain rate. More precisely, we have

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}(\boldsymbol{\nabla u}, P) = -P\boldsymbol{I} + 2\mu \boldsymbol{D}(\boldsymbol{\nabla u}) = -P\boldsymbol{I} + \mu(\boldsymbol{\nabla u} + \boldsymbol{\nabla u}^T) \tag{56}$$

where P is the pressure, I is the identity matrix, μ *is the dynamic viscosity of the fluid and is a positive quantity. The term* $2\mu \boldsymbol{D}(\boldsymbol{\nabla u})$*is the viscous stress component of the stress tensor. We have that [P]=*

N/m^2 and $[\mu]$= kg/ms. The viscosity may vary, for example it may depend on the fluid temperature. The assumption of Newtonian fluid, however, implies that μ is independent of kinematic quantities. ***Simple models for non-Newtonian fluids, often used for blood flow simulations, express the viscosity as function of the strain rate, that is*** $\mu = \mu(\boldsymbol{D}(\boldsymbol{u}))$.

4 General

Overview Non-Newtonian Properties of Blood

Overview Non-Newtonian Models

Resume

1. In certain regions (e.g. low shear regions: e.g. near bifurcations, graft anastomoses, stenoses, and aneurysm) the Non-Newtonian behaviour of blood shound not be neglected and integrated into the model equation
2. Hemorheology is characterized by four non-Newtonian characteristics
   (a) a **shear thinning viscosity**
   (b) a general **viscoelastic** response to transient flow deformations and
   (c) a **non-zero yieldstress** with
   (d) associated **thixotropy**
3. Starting point for the flow analysis is in a macroscopic viewpoint the continuity equation and momentum equation
4. In order to account for Non-Newtonian effects, we can
   (a) use linear elastic constitutive equation to close system and make the viscosity dependent of the deformation rate tensor (Generalized non-Newtonian equations e.g. Power law)
   (b) use a (nonlinear) viscoelastic constitutive equation $\Rightarrow$ more complex constitutive equations must be solved simultaneously along with the equations of conservation of mass and momentum.
5. Generalized non-Newtonian equations can capture a) shear thinning and c) yield stress. They are computationally inexpensive to implement but cannot predict accurately transient (thixotropic/ hysteretic) changes in the viscosity which are relevant as blood flows naturally under pulsatile conditions.
6. To better account for the transient effects, a viscoelastic model can be used. Viscoelastic models can account for elasticity in the sample and can predict non-shear components of the stress tensor. However, they are typically unable to capture thixotropic effects that blood demonstrates associated with the structural evolution.
7. Thixotropic models to describe the transient rheology of blood

Questions

- *"Capillaries, the smallest blood vessels, are very different in their properties and connectivity. Capillaries can be as small as 5 micrometer diameter, which is considerable smaller than the largest diameter of a red blood cell." (Preface Book Cardiovascular mathematics)*
  "Things get even more complex in the smallest capillaries, since here the size of a red blood cell becomes comparable to that of the vessel and the continuum hypothesis may become questionable" (Chapter 2 Book Cardiovascular mathematics)
  but *"Blood flow on scales larger than 300μm is consistently modeled as a continuous fluid, as it is computationally more convenient because models no longer include the individual cell dynamics [20,24,25]"*(A heterogeneous multi-scale model for blood flow)
  What is the relevant diamter which we want to examine?
  Possible locations where the non-Newtonian behaviour will be significant include segments of the venous system and stable vortices downstream of some stenoses and in the sacs of some aneurysms In summary, we can conclude that blood is generally a non-Newtonian fluid, which can however be regarded as a Newtonian fluid to model blood flow in arteries with diameters larger than 100 μm where measurements of the apparent viscosity show that it ranges from 0.003 to 0.004 Pa.s and the typical Reynolds number is about 0.5 (see Methods of Blood Flow Modelling).
  What are our regions of interest?
  "A simple model of a straight rigid blood vessel with unsteady periodic flow is considered. A numerical solution that considers the fully coupled Navier Stokes and energy equations is used for the simulations"(A review on rheology of non-Newtonian properties of blood)
  Heat transfer? Are we looking for these kind of phenomena?

  QUESTION: Do we want to examine a specific phenomena (e.g aneurysma) s.t. we can focus from the variety of non-newtonian models (shear thinning, plasticity, viscoelasticity, thixotropy, all together, etc.) on a specific group

- In a An Overview of Some Mathematical Models of Blood Rheology the importance of Platelet activation and blood coagulation is discussed - *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 ...*
  I will neglect biochemical processes?

- Rather genereal question:((*"At a macroscopic level, the arterial wall is a complex multi-layer structure which deforms under the action of blood flow. Even though sophisticated constitutive equations have been proposed for the structural behaviour of the vessel wall, its elastic characteristics in vivo are still very difficult to determine and are usually inferred from pulse propagation data. The modelling of the interaction between blood flow and the vessel wall mechanics needs algorithms which correctly describe the energy transfer between them to accurately represent wave propagation phenomena." (Preface Book Cardiovascular mathematics)*
  How far is the development of Trilions FSI-code?))