

HEMORREOLOGIA E MODELOS MATEMÁTICOS / HEMORHEOLOGY AND MATHEMATICAL MODELS

Adélia Sequeira¹

ABSTRACT

This paper is devoted to a critical review of blood rheology and constitutive models for blood based on phenomenological considerations. The relationship between the multiphase properties and the mechanical characteristics of blood, including shear thinning viscosity, yield stress, thixotropy and viscoelasticity is considered. The significance of the non-Newtonian behavior of blood in the circulation is also addressed.

Key-words: Blood rheology, mathematical models, shear thinning, yield stress, thixotropy, viscoelasticity.

INTRODUCTION

Hemorheology is the science of deformation and flow of blood and its formed elements. This field involves the investigation of both the macroscopic behavior of blood using rheometric experiments as well as its microscopic properties *in vitro* and *in*

vivo. It also involves studies of the interactions among blood cellular elements and between these components and the endothelial cells that line blood vessels.

The blood circulation in the cardiovascular system depends not only on the driving force of the heart and the architecture and mechanical properties of the vascular system, but also on the mechanical properties of blood itself. Whole blood is a concentrated suspension of formed cellular elements including red blood cells (RBCs) or erythrocytes, white blood cells (WBCs) or leukocytes and platelets or thrombocytes. The non-Newtonian behavior of blood is largely due to three characteristics of the erythrocytes: their ability to form aggregates (three-dimensional microstructures) when at rest or at low shear rates, their deformability, and their tendency to align in the flow direction at high shear rates. A transition in microstructure is found between these two regimes^{1,2}. The shape of the erythrocytes can change (deform) both due to in plane stretch-

¹ Departamento de Matemática e CEMAT
Instituto Superior Técnico, Lisboa, Portugal
adelia.sequeira@math.ist.utl.pt

ing of its membrane as well as from bending³.

As will be elaborated below, blood displays a shear thinning viscosity, viscoelasticity, thixotropy and possibly a yield stress. An understanding of the coupling between the blood composition and its physical properties is essential for developing suitable constitutive models to describe blood behavior.

Advances in the field of hemorheology are based on the evidence that they might be the primary cause of many cardiovascular diseases. In fact, hemorheological aberrations can easily be considered as a result (or an indicator) of insufficient circulatory function. Basically, pathologies with hematological origin like leukemia, hemolytic anemia, thalassemia or pathologies associated with the risk factors of thrombosis and atherosclerosis like myocardial infarction, hypertension, strokes or diabetes are mainly related to disturbances of local homeostasis. Therefore, the mathematical and numerical study of powerful, yet simple, constitutive models that can capture the rheological response of blood over a range of flow conditions is ultimately recognized as an important tool for clinical diagnosis and therapeutic planning (see e.g.^{4,5}).

To better interpret and analyze the experimental data on blood it is helpful to turn to the literature on the rheology of particle suspensions. For rigid particles, a vast amount of published literature exists (see e.g.⁶). However, the study of suspensions of multiple, interacting and highly deformable particles such as blood, has received less attention and presents a challenge for both theoretical

and computational fluid dynamicists, (e.g.⁷).

The aim of this paper is to present a brief overview of the rheological properties of blood, including its non-Newtonian characteristics, and review some of the macroscopic mathematical models that have been proposed in the literature to model these features.

PHYSICAL MECHANISMS BEHIND THE MECHANICAL PROPERTIES OF BLOOD

In this section we briefly discuss the physical mechanisms of erythrocytes that have the strongest influence on the non-Newtonian behavior of whole flowing blood at low shear rates.

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 (3-D) aggregates⁸. The biochemical process of *rouleaux* formation is still unclear. It has been experimentally observed that these stacks will not form if the erythrocytes have been hardened or in the absence of fibrinogen and globulins.

For blood at rest, the 3-D structure formed by the RBCs looks solid-like, appearing to resist flow until a finite level of force is applied. The applied stress needed to initiate flow, e.g. in simple shear, is often referred to as

the yield stress and, under normal conditions, is primarily a function of the hematocrit and the fibrinogen concentration of the plasma⁹. Additional factors such as the red cell shape, deformability and tendency to aggregate also influence the value of the yield stress parameter. As discussed below, the existence of a yield stress for fluids in general and treatment of this yield stress as a material parameter is a controversial issue (see, e.g.,^{10,11}).

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. In the studies of Schmid-Schönbein⁸ at shear rates between 5.8 and 46 s⁻¹ each doubling of the shear rate resulted in a decrease in average aggregate size of approximately 50% (see also¹² for further discussion).

Once the chains are broken down to 4-10 cells, they are resistant to further shearing and, at high shear rates they roll, rotate and tumble as units along with individual cells, and the structure visibly recoils elastically. A critical shear rate $\dot{\gamma}_{\max}$ is defined as a constant shear rate at which, effectively there are no more aggregates (larger than 15 μm). In whole blood from healthy humans, different values are reported for this critical shear rate, largely in the range of 5-100 s⁻¹. Dintenfass [4] attributed this variation in reported values to the degree of aggregation of the original sample which, as discussed later, is consistent with the thixotropic nature of blood¹³.

In diseased states, the critical shear rate can increase substantially. For example, in blood samples from patients with acute myocardial infarctions, the critical shear rate for dispersion was found to be greater than approximately 250 s⁻¹ and the average aggregate size was larger than in the controls for all shear rates^{8,14}.

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 microstructure¹⁴. The finite time necessary for equilibrium of the structure to be reached (both during aggregation and disaggregation) is responsible for the thixotropic behavior of blood at low shear rates (see e.g.¹⁵). 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 (e.g.⁴). For example, in a cone and plate viscometer, for shear rates between 0.01 and 1.0 s⁻¹ the equilibrium distributions were found to be reached after time intervals of 20 to 200 seconds.

Accelerating flow has a marked effect on the structure of the aggregate. Under acceleration between fixed shear rates, significant elongation of rouleaux occurs which is not seen when the flow is held at a fixed shear rate. The elongation is particularly evident in rouleaux that bridge larger secondary structures and is found to arise from realignment of the individual cells (sliding of the cells from a parallel stack to a sheared stack) and deformation of individual cells (ellipsoidal defor-

mation and eventually prolate deformation). As a result of these mechanisms, the aggregate length can increase up to three fold⁸. Under a sinusoidal variation of shear, elastic behaviour of the aggregates is observed (e.g.^{2,16}). While typical data for whole blood viscosity are obtained from quasi-static shear experiments, small amplitude oscillatory shear experiments are used to measure both viscous and elastic properties in the regime of small deformations from the rest history.

In a Couette rheometer, when blood is subjected to a constant shear rate slightly above $\dot{\gamma}_{\max}$, the cells can be seen to rotate. With increasing shear rate, they rotate less and for shear rates above 230 s^{-1} they cease to rotate and remain aligned with the flow direction⁸.

For shear rates above 400 s^{-1} the tumbling of the individual cells is completely absent, 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. Close observation suggests that the changing cells contours are consistent with a tank-treading motion of the cells membranes about their interior, similar to a fluid drop deformation^{2,17}. 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.

MECHANICAL PROPERTIES OF BLOOD

Measurements of the mechanical properties of whole blood are technically challenging, particularly at low to medium shear rates where denatured protein films, sedimentation and phase separation can lead to erroneous results. At high shear rates, inertial effects can be problematic. As a result, measuring the mechanical properties of blood over a wide range of shear rates (e.g. $0.01 - 500 \text{ s}^{-1}$), can require the use of more than one rheometer. The three most commonly used rheometers for blood are the concentric cylinder rheometer (Couette rheometer), the cone and plate rheometer, and the capillary rheometer. These devices can be used in steady and oscillatory modes to measure the viscosity and linear viscoelastic properties of blood, respectively. An overview of typical blood rheometers and a discussion of some of the challenges which are particular to blood rheometry can be found in^{12,15}.

Viscosity of blood

The most well studied non-Newtonian characteristic of blood is its diminishing viscosity with increasing shear rate, called shear thinning behavior.

As discussed earlier, the mechanical properties of blood are dominated by the 3-D microstructure formed by the RBCs and general distribution of RBCs in the flowing plasma. At lower shear rates, the behavior is controlled by the effect of the 3-D RBC formations on the flow and the ability of these formations to deform and store

energy. At moderate to high shear rates, these cells are dispersed in the plasma and the properties of the blood are then influenced by their tendency to align and form layers in the flow, as well as their deformation. The importance of RBCs aggregation on blood viscosity at low shear rates was clearly demonstrated by Chien¹⁸ who compared the viscosity of RBCs suspended in heparinized plasma and albumin-Ringer solution (Alb). The normal RBCs aggregation found in plasma does not occur in Alb. Though the viscosity of plasma and Alb were both the same, the viscosity of the RBCs' solution was greatly increased at low shear rates by RBCs aggregation (less than approximately 5 s^{-1}) but unaffected at larger shear rates.

The effect of RBCs deformability on viscosity of suspensions of these cells was also clearly shown in¹⁸. Chien compared the viscosity of normal RBC in Alb and that of hardened RBC in Alb (presumably at zero shear rate). The ability of normal RBC to deform (change shape and stretch) significantly decreased the viscosity over all shear rates tested. Fig. 1 displays the shear thinning behavior of whole blood as experimentally observed by Chien¹⁸. Each of these data points represents an equilibrium value obtained at a fixed shear rate.

In addition to shear rate, the aggregate size is a function of cell shape, plasma composition and hematocrit. This is reflected in the dependence of viscosity on these same variables. We do not address quantitative results for these variables here, but refer the reader to references such as^{4,19}. Moreover, the viscosity of whole blood is strongly dependent on temperature.

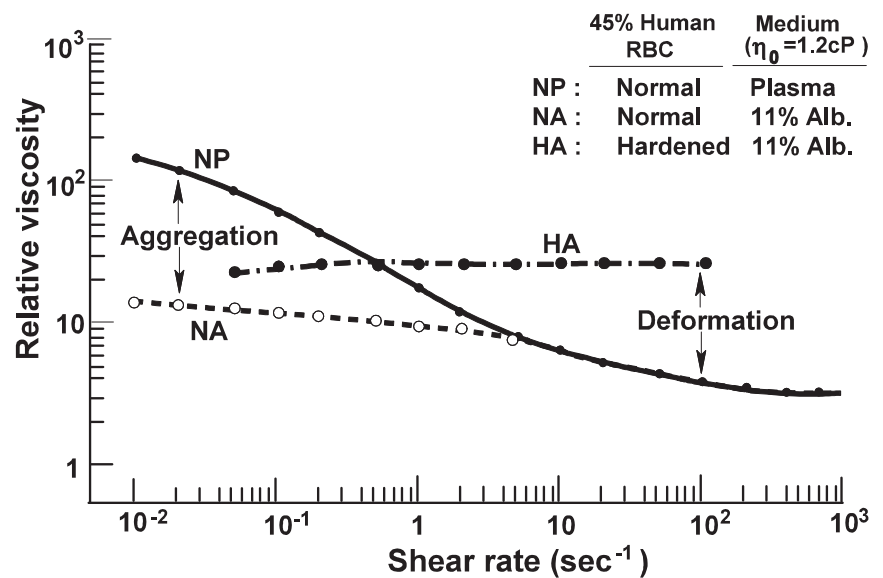


Fig. 1 – Variation of the relative viscosity as a function of the shear rate for normal RBC in heparinized plasma (NP), normal RBC in albumin-Ringer solution (NA) and hardened RBCs in albumin-Ringer solution (HA) at a temperature of 37°C , hematocrit $H_t=45\%$ using a Couette viscometer (reproduced from Chien [18], with permission)

Merrill *et al.*²⁰ found the dependence of blood viscosity on temperature to be similar to that of water for temperatures ranging from 10 to 40°C and shear rates from 1 to 100 s^{-1} . The variation of plasma viscosity with temperature is also known to approximately follow that of water²¹. For these reasons, blood viscosity is often reported relative to the viscosity of plasma or water at the same temperature.

Viscoelasticity and thixotropy of blood

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 reversible deformation of the RBCs 3D microstructures²². Elastic energy is due to the properties of the RBC membrane and the bridging mechanisms within the 3D structure. It can also be stored in

the deformation of individual RBC, though this is not believed to play an appreciable role unless the RBC concentration is significantly elevated above normal physiological levels²³. However, these properties are of relatively small magnitude and to date 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.

The reader is referred to²² for a review of the dependence of blood viscoelasticity on factors such as temperature, hematocrit and RBC properties.

While the linear viscoelastic functions are relatively straightforward to obtain in the rheometers referred above, it should be emphasized that blood flow in the circulatory system is rarely in the regime applicable for linear viscoelasticity theory. The linear elastic material constants are indicative of aspects of the microstructure and therefore can be used as a method of quantifying blood properties. However, ultimately, there is a need to consider the finite viscoelastic behavior of blood, if viscoelastic constitutive equations are going to be used to model blood behavior in the circulatory system.

The formation of the three-dimensional microstructure and the alignment of the RBCs are not instantaneous, which gives blood its thixotropic behavior. 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 3-D structure of blood to form and breakdown²⁴.

Yield stress of blood

The behavior of a number of 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 material property (constant) of the fluid. An extensive description of methods for measuring yield stress is given in²⁵. Briefly, there are two categories of methods: indirect methods and direct methods. In indirect methods, the shear stress versus shear rate curve is back extrapolated to zero, possibly using a specific constitutive model or simple linear approximation. Sometimes the yield stress is set to the lowest measured shear stress²⁶. In direct methods, an attempt is made to directly measure the shear stress at which the fluid begins to flow.

Reported values for the yield stress of blood vary greatly ranging from 0.002 to 0.40 dynes/cm², see e.g.⁴. This variation has been attributed to artifacts arising from interactions between the RBCs and surfaces of the rheometer²¹ as well as the experimental method used to measure the yield stress.

The large range seen for blood is consistent with results for other fluids where this spread is attributed to the experimental methodology, the criterion used to define the yield stress, and the length of time over which the experiment is run²⁴. A true material constant should be independent of these factors and these results have called into serious question the treatment of the yield stress as a material parameter. Dintenfass⁴ appears to be

the first to question the appropriateness of such a material constant for blood. He suggested that rather than treating the yield stress as a constant, it should be considered as a function of time. This time dependence is consistent with the link between yield stress and thixotropy proposed years later by other researchers²⁷.

CONSTITUTIVE MODELS FOR BLOOD

As discussed earlier, the presence of the formed elements in blood leads to some significant and fascinating changes in its rheological properties. In this section, we discuss constitutive models introduced to capture one or more of these properties.

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. Thus the models presented here are not appropriate in the capillary network. For an overview of hemorrheology in the microcirculation we refer the reader to the review articles of Popel and Johnson²⁸ and Pries and Secomb²⁹.

Since both the shear thinning and viscoelastic properties diminish rapidly as the 3D microstructure of RBCs breaks down, it is important to consider in which flow regimes and clinical situations the non-Newtonian properties of blood will be important. RBCs would need to be subjected to shear rates below 1 s^{-1} per period sufficient for these structures to form and alter the flow. Schmid–Schönbein and co-workers³⁰ found the half-time for aggregate formation to be

3-5 s for normal blood and 0.5-1.5 s for pathological blood samples. In their experiments, the time for aggregation was measured after samples were exposed to an abrupt drop in shear rate from 460 s^{-1} to approximately zero.

The blood circulation time for humans is on the order of minutes, so for normal blood, the RBC structure will be broken down in the majority of the arterial system and only exist in regions of the circulation where there are stable recirculation zones with shear rates significantly below 1 s^{-1} (see¹² for more details).

Possible locations where the non-Newtonian behavior will be significant include segments of the venous system and stable vortices downstream of some stenosis and in the sacs of some aneurysms. For various pathologies, the 3D microstructure formed by the RBC is substantially stronger than for normal blood. For these patients, it is possible the 3D microstructure will exist in more widespread regions of the circulatory system. Increased RBC aggregation has been observed for patients with infections, trauma, burns, diabetes mellitus, AIDS and other diseases³¹. The quantification of the mechanical response of blood (shear thinning, viscoelasticity) can also be important for patient diagnosis²².

As a first step towards the macroscopic modeling of blood flow we consider the equations given by

$$\rho \frac{\partial u}{\partial t} + \rho(u \cdot \nabla)u = -\nabla p + \nabla \cdot \tau \quad (1)$$

$$\nabla \cdot u = 0$$

in a domain $\Omega \subset R^3$ representing the lumen of the vessel. These equations express the conservation of linear

momentum and mass (or incompressibility condition) for isothermal flows and are completed with appropriate initial and boundary conditions. Here $u(x,t)$ and $p(x,t)$ denote the blood velocity and pressure in Ω , with $t \geq 0$, ρ is the blood density and τ is the extra-stress tensor accounting for differences in behavior from a purely inviscid, incompressible fluid. To close system (1) we require a constitutive equation relating the state of stress to the kinematic variables such as rate of deformation of fluid elements. The aim of this section is to review some of the macroscopic models suitable for blood flow under certain flow conditions.

Generalized Newtonian and yield stress models

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

$$\tau = 2\mu D \quad (2)$$

where μ is the (constant) viscosity and $D = (\nabla u + \nabla u^T) / 2$ is the rate of deformation tensor. The substitution of (2) in the linear momentum equation (1) leads to the well-known Navier-Stokes equations for an incompressible viscous fluid. As already discussed this set of equations is commonly used with some justification to describe blood flow in the heart and 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.

The most general constitutive model of the form $\tau = \tau(\nabla u)$ which satisfies invariance requirements³² can be written as

$$\tau = \varphi_1(II_D, III_D)D + \varphi_2(II_D, III_D)D^2 \quad (3)$$

where II_D and III_D are the second and third principal invariants of D

$$II_D = \frac{1}{2}((trD)^2 - tr(D^2)), \quad III_D = detD$$

And $trD \equiv 0$ for isochoric motions. Incompressible fluids of the form (3) are called Reiner-Rivlin fluids. They include Newtonian fluids as a particular case, corresponding to φ_1 constant and $\varphi_2 \equiv 0$.

The behavior of real fluids impose some restrictions on the material functions φ_1 and φ_2 . In fact, there is no evidence of real fluids with non-zero values of φ_2 and the dependence on the value of III_D is often neglected³². As a result, attention is usually restricted to a special class of Reiner-Rivlin fluids called generalized Newtonian fluids, for which

$$\tau = 2\mu(\dot{\gamma})D \quad (4)$$

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

$$\dot{\gamma} \equiv \sqrt{2tr(D^2)} = \sqrt{-4II_D} \quad (5)$$

and $\mu(\dot{\gamma})$ is a shear dependent viscosity function (for isochoric motions II_D is not a positive quantity).

One of the simplest generalized Newtonian fluids is the *power-law*, for which the viscosity function is given by

$$\mu(\dot{\gamma}) = K\dot{\gamma}^{n-1} \quad (6)$$

where the positive constants n and K are termed the power-law index and consistency, respectively. This model includes, as a particular case, the constant viscosity fluid (Newtonian) when $n=1$. For $n<1$ it leads to a monotonic decreasing function of the shear rate (shear thinning fluid) and 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 $(\dot{\gamma}) \rightarrow \infty$, which is unphysical.

One of the most successful viscosity laws for blood is an extension of the power-law model due to Walburn and Schneck³³. In addition to the shear rate, they considered the dependence of the viscosity on the hematocrit (Ht) and total protein minus albumin ($TPMA$) content through the parameter K and n in (6). Using a nonlinear regression analysis they found that shear rate and hematocrit were the two most important factors in decreasing order of importance. Based on these two factors, they formulated the following expressions of K and n ,

$$K = C_1 \exp(C_2 Ht), \quad n = 1 - C_3 Ht \quad (7)$$

Fig. 2 shows a comparison of viscosity functions $\mu(\dot{\gamma})$ for the power-law model (6) using material constants provided by Kim *et al.*³⁴ (Kim) and Liepsch and Moravec³⁵ (LM) for human blood. Representative viscosity curves for the Walburn-Schneck model (WS)³³ with factors depending

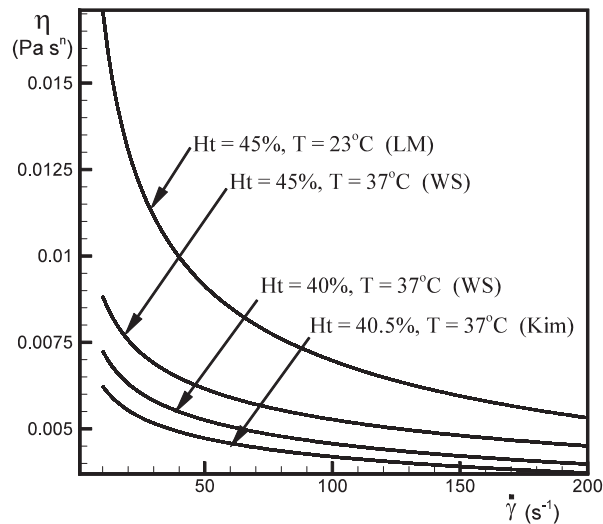


Fig. 2 – Comparison of viscosity functions $\mu(\dot{\gamma})$ for the power-law model (6) using material constants provided obtained by curve fit to experiments.

on hematocrit (7) are also shown. The viscosity functions obtained from³³ and³⁴ for $Ht = 40\%$ are quite close. In contrast, those in³⁴ and³⁵ for $Ht = 45\%$ are substantially different, likely due to the lower temperatures used in³³ compared to those in³⁵.

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

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

or, in non-dimensional form as

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

Here μ_0 and μ_∞ are the asymptotic viscosity values at zero and infinite shear rates and $F(\dot{\gamma})$ is a shear dependent function, satisfying the following natural limit conditions

$$\lim_{\dot{\gamma} \rightarrow 0^+} F(\dot{\gamma}) = 1 \quad \text{and} \quad \lim_{\dot{\gamma} \rightarrow \infty} F(\dot{\gamma}) = 0$$

Different choices of the function $F(\dot{\gamma})$ correspond to different models

Table 1 – Material constants for various generalized Newtonian models for blood

Model	Non-Newtonian viscosity	Material constants for blood
Power Law	$\mu(\dot{\gamma}) = K\dot{\gamma}^{n-1}$	$n = 0.61, K = 0.42$
Powell-Eyring	$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = \frac{\sinh^{-1}(\lambda\dot{\gamma})}{\lambda\dot{\gamma}}$	$\mu_0 = 0.056Pas, \mu_\infty = 0.00345Pas$ $\lambda = 5.383s$
Cross	$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = \frac{1}{1 + (\lambda\dot{\gamma})^m}$	$\mu_0 = 0.056Pas, \mu_\infty = 0.00345Pas$ $\lambda = 1.007s, m = 1.028$
Modified Cross	$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = \frac{1}{(1 + (\lambda\dot{\gamma})^m)^a}$	$\mu_0 = 0.056Pas, \mu_\infty = 0.00345Pas$ $\lambda = 3.736s, m = 2.406, a = 0.254$
Carreau	$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = (1 + (\lambda\dot{\gamma})^2)^{(n-1)/2}$	$\mu_0 = 0.056Pas, \mu_\infty = 0.00345Pas$ $\lambda = 3.313s, n = 0.3568$
Carreau-Yasuda	$\frac{\mu(\dot{\gamma}) - \mu_\infty}{\mu_0 - \mu_\infty} = (1 + (\lambda\dot{\gamma})^a)^{(n-1)/a}$	$\mu_0 = 0.056Pas, \mu_\infty = 0.00345Pas$ $\lambda = 1.902s, n = 0.22, a = 1.25$

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.

Table 1 summarizes some of the most common generalized Newtonian models that have been considered in the literature for the shear dependent viscosity of whole human blood. Values for the material constants given in this table were obtained by Cho and Kensey³⁶ for a compilation of human and canine blood (*Ht* ranging from 33-45%), using a nonlinear least squares analysis.

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 $\sqrt{|II_\tau|} = \tau_y$, where II_τ is the second invariant of the extra stress tensor τ . The most common yield stress model for blood is the Casson's model³⁷ which, in simple shear has the form

$$\sqrt{|II_\tau|} < \tau_y \Rightarrow D = 0$$

$$\sqrt{|II_\tau|} \geq \tau_y \Rightarrow \begin{cases} D = \frac{1}{2\mu_N} \left(1 - \frac{\sqrt{\tau_y}}{\sqrt{|II_\tau|}} \right) \tau \\ \tau = 2 \left(\sqrt{\mu_N} + \frac{\sqrt{\tau_y}}{\sqrt{4|II_\tau|}} \right)^2 D \end{cases}$$

The Newtonian constitutive equation is a special case of the Casson equation with τ_y set to zero, in which case μ_N is the Newtonian viscosity. Through this model blood behaves rigidly until the yield criterion is satisfied, after which it displays a shear thinning behavior.

Other yield stress models like Bingham or Herschel-Bulkley models are also used for blood (see e.g.^{12,15}) as well as the constitutive model developed by Quemada³⁸ using a semi-phenomenological approach, with the apparent viscosity given by

$$\mu(\dot{\gamma}) = \mu_F \left(1 - \frac{1}{2} \frac{k_0 + k_\infty \sqrt{\dot{\gamma} / \dot{\gamma}_c}}{1 + \sqrt{\dot{\gamma} / \dot{\gamma}_c}} \varphi \right)^{-2}$$

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, respectively.

As discussed earlier, the existence of a yield stress and its use as a material parameter is a controversial issue, since 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 time²⁷.

Viscoelastic and thixotropic models

None of the models in the previous section accounts for either the viscoelasticity or the thixotropy of blood. 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

$$\tau + \lambda_1 \frac{\delta\tau}{\delta t} = 2\mu D \quad (8)$$

where λ_1 is the relaxation time and $\delta(\cdot)/\delta t$ stands for the so-called *convected derivative*, a generalization of the material time derivative, chosen so that $\delta\tau/\delta t$ is objective under a superposed rigid body motion and the resulting second-order tensor is symmetric¹⁵.

A more general class of rate type models, called *Oldroyd type* models, are defined by

$$\tau + \lambda_1 \frac{\delta\tau}{\delta t} = 2\mu \left(D + \lambda_2 \frac{\delta D}{\delta t} \right) \quad (9)$$

where the material coefficient λ_2 denotes the retardation time 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 two models (2) and (8) as particular cases.

Thurston³⁹ was among the earliest to recognize the viscoelastic nature of blood and that the viscoelastic behavior is less prominent with increasing shear rate. He proposed a generalized Maxwell model that was applicable to one dimensional flow simulations

and observed later that, beyond a critical shear rate, the nonlinear behavior is related to the microstructural changes that occur in blood⁴⁰. Thurston's work was suggested to be more applicable to venous or low shear unhealthy blood flow than to arterial flows. Recently, a generalized Maxwell model related to the microstructure of blood, inspired on the behavior of transient networks in polymers, and exhibiting shear thinning, viscoelasticity and thixotropy, has been derived by Owens⁴¹.

Other viscoelastic constitutive models of differential type, suitable for describing blood rheology have been proposed in the recent literature. The empirical three constant generalized Oldroyd-B model studied in⁴² belongs to this class. It has been obtained by fitting experimental data in one dimensional flows and generalizing such curve fits to three dimensions. This model captures the shear thinning behavior of blood over a large range of shear rates but it has its limitations, given that the relaxation times do not depend on the shear rate, which does not agree with experimental observations. The model developed by Anand and Rajagopal⁴³ in the general thermodynamic framework stated in⁴⁴ includes relaxation times depending on the shear rate and gives good agreement with experimental data in steady Poiseuille and oscillatory flows.

CONCLUSIONS

In this short review the material properties of human blood and in particular its shear viscosity, elasticity and thixotropy have been discussed

in terms of the complex evolving microstructure, and especially of the deforming and migrating red blood cells in their different states of aggregation. We conclude that the most promising rheological models are those developed from an underlying microstructure similar to that of blood. Some existing gaps can be identified as significant challenges for the development of new rheological models to be used in large-scale numerical simulations.

1. Although attention has been devoted to the measurement of some of the basic macroscopic rheological properties of blood, especially in flow regimes where non-Newtonian effects are most likely to be observed, there is urgent need for further experimental data to validate the current rheological models and provide a rational basis for the further development of microstructural models.

2. The transition from the non-Newtonian to the Newtonian viscosity character of blood should be better investigated, since a variation on the critical value of the shear rate appears in literature to address this issue. The availability of reliable measurements of quantities such as the velocity, wall shear stress and pressure in well characterized physiological flows (*in vivo*) is essential in CFD studies of blood flow in the cardiovascular system.

3. A suitable account of the mathematical structure of the systems of equations derived from the constitutive models for blood must be considered. These systems, closed with appropriate initial and boundary conditions, are highly nonlinear and the development of well adapted stable, accurate and affordable numerical

methods is of the greatest importance. Parallel algorithms and fast large-scale computing platforms, opening up new possibilities in simulation and visualization, become crucial when using non-Newtonian solvers for blood.

Acknowledgement: This work has been partially supported by the Project PTDC/MAT/68166/2006 and by the Center of Mathematics and its Applications – CEMAT/IST through FCT's Funding Program.

REFERENCES

1. S. Chien, S. Usami, R. J. Dellenback, M. I. Gregersen. Shear-dependent deformation of erythrocytes in rheology of human blood. *Am. J. Physiol.*, 219:136-142, 1970.
2. H. Schmid-Schönbein, R. Wells. Fluid drop-like transition of erythrocytes under shear. *Science*, 165:288-291, 1969.
3. S. Chien. Red cell deformability and its relevance to blood flow. *Ann. Rev. Physiology*, 49:117-192, 1987.
4. L. Dintenfass. *Blood Microrheology – Viscosity Factors in Blood Flow, Ischaemia and Thrombosis*. Butterworth, 1971.
5. G. D. O. Lowe. *Clinical Blood Rheology*, Vol. I, II. CRC Press, Boca Raton, Florida, 1998.
6. M. C. Roco (Ed.) *Particulate Two-Phase Flow*. Series in Chemical Eng. Butterworth-Hinemann Publ., 1993.
7. V. Cristini, G.S. Kassab. Computer modeling of red blood cell rheology in the microcirculation: A brief overview. *Ann. Biomed. Eng.*, 33(12):1724-1727, 2005.
8. H. Schmid-Schönbein, R. Wells. Rheological properties of human erythrocytes and their influence upon anomalous viscosity of blood. *Physiology Rev.*, 63:147-219, 1971.
9. E. W. Merrill. Rheology of blood. *Physiol. Rev.*, 49:863-888, 1969.
10. H. A. Barnes, K. Walters. The yield stress myth? *Rheol. Acta*, 24:323-326, 1985.
11. P. C. F. Moller, J. Mewis, D. Bonn. Yield stress and thixotropy: on the difficulty of measuring yield stress in practice. *Soft Matter*, 2:274-288, 2006.
12. A. M. Robertson, A. Sequeira, M. Kameneva. Hemorreology. In: *Hemodynamical Flows: Modeling, Analysis and Simulation*, Series: Oberwolfach Seminars, Vol. 37, 63-120, Galdi, G.P. et al, Birkhäuser, 2008.
13. A. Barnes. Thixotropy – a review. *J. Non-Newtonian Fluid Mech.*, 70:1-33, 1997.
14. J. Goldstone, H. Schmid-Schönbein, R. Wells. The rheology of red blood cell aggregates. *Microvas. Res.*, 2:273-286, 1970.

15. A. M. Robertson. Review of relevant continuum mechanics. In: *Hemodynamical Flows: Modeling, Analysis and Simulation*, Series: Oberwolfach Seminars, Vol. 37, 63-120, Galdi, G.P. et al, Birkhäuser, 2008.
16. A. L. Copley, R. G. King, S. Chien, S. Usami, R. Skalak, C. R. Huang. Microscopic observations of viscoelasticity of human blood in steady and oscillatory shear. *Biorheology*, 12:257-263, 1975.
17. T. M. Fischer, M. Stöehr-Lissen, H. Schmid-Schönbein. The red cell as a fluid droplet: tank tread-like motion of human erythrocyte membrane in shear flux. *Science*, 202:894-896, 1978.
18. S. Chien. Shear dependence of effective cell volume as a determinant of blood viscosity. *Science*, 168:977-979, 1970.
19. R. L. Whitmore. *Rheology of the Circulation*. Pergamon Press, 1968.
20. E. W. Merrill, E. R. Gilliland, G. Cokelet, H. Shin, A. Britten, R. E. Wells, Jr. Rheology of human blood, near and at zero flow. Effects of temperature and hematocrit level. *Biophys. J.*, 3:199-213, 1963.
21. S. E. Charm, G. S. Kurland. *Blood Flow and Microcirculation*. John Wiley & Sons, 1974.
22. G. B. Thurston. Viscoelastic properties of blood and blood analogs. *Advances in Hemodynamics and Hemorrheology*, 1:1-30, 1996.
23. S. Chien, R. G. King, R. Skalak, S. Usami, A. L. Copley. Viscoelastic properties of human blood and red cell suspensions. *Biorheology*, 12:341-346, 1975.
24. H. A. Barnes. Thixotropy – a review. *J. Non-Newtonian Fluid Mech.*, 70:1-33, 1997.
25. Q. D. Nguyen, D. V. Boger. Measuring the flow properties of yield stress fluids. *Annual Reviews*, pages 47-88, 1992.
26. C. Picart, J.M. Piau, H. Galliard, P. Carpentier. Human blood shear yield stress and its hematocrit dependence. *J. Rheol.*, 42:1-12, 1998.
27. P. C. F. Moller, J. Mewis, D. Bonn. Yield stress and thixotropy: on the difficulty of measuring yield stress in practice. *Soft Matter*, 2:274-288, 2006.
28. A. S. Popel, P. C. Johnson. Microcirculation and hemorrheology. *Annu. Rev. Fluid Mech.*, 37:43-69, 2005.
29. A. R. Pries, T. W. Secomb. Rheology of the microcirculation. *Clin. Hemorheol. Microcirc.*, 29:143-148, 2003.
30. H. Schmid-Schönbein, E. Volger, H. J. Klose. Microrheology and light transmission of blood. II– The photometric quantification of red cell aggregation formation and dispersion in flow. *Pflügers Arch.*, 333:140-155, 1972.
31. G. D. O. Lowe, Ed., *Clinical Blood Rheology*, Vol. I and II. CRC Press, Boca Raton, Florida, 1998.
32. G. Astarita, G. Marrucci. *Principles of Non-Newtonian Fluid Mechanics*. McGraw Hill, 1974.
33. F. J. Walburn, D. J. Schneck. A constitutive equation for whole human blood. *Biorheology*, 13:201-210, 1976.
34. S. Kim, Y.I. Cho, A.H. Jeon, B. Hogenauer, K.R. Kensey. A new method for blood viscosity measurement. *J. Non-Newtonian Fluid Mech.*, 94:47-56, 2000.
35. D. Liepsch, St. Moravec. Pulsatile flow of non-Newtonian fluid in distensible models of human arteries. *Biorheology*, 21:571-586, 1984.
36. Y. I. Cho and K. R. Kensey. Effects of the non-Newtonian viscosity of blood on flows in a diseased arterial vessel. Part I: Steady flows. *Biorheology*, 28:241-262, 1991.
37. G. W. Scott Blair. An equation for the flow of blood, plasma and serum through glass capillaries. *Nature*, 183:613-614, 1959.
38. D. Quemada. Rheology of concentrated disperse systems III. General features of the proposed non-Newtonian model. Comparison with experimental data. *Rheological Acta*, 17:643-653, 1978.
39. G.B. Thurston. Viscoelasticity of human blood. *Biophysical J.*, 12:1205-1217, 1972.
40. G.B. Thurston. Non-Newtonian viscosity of human blood: Flow induced changes in microstructure. *Biorheology*, 31(2):179-192, 1994.
41. R.G. Owens. A new microstructure-based constitutive model for human blood. *J. Non-Newtonian Fluid Mech.*, 14:57-70, 2006.
42. K. K. Yeleswarapu, M.V. Kameneva, K. R. Rajagopal, J. F. Antaki. The flow of blood in tubes: Theory and experiment. *Mechanics Research Communications*, 25(3):257-262, 1998.
43. M. Anand, K. R. Rajagopal. A shear thinning viscoelastic fluid model for describing the flow of blood. *Int. J. Cardiovascular Medicine and Science*, 4:59-68, 2004.
44. K. R. Rajagopal, A. R. Srinivasa. A thermodynamic framework for rate-type fluid models. *88:207-227*, 2000.