Overview of Mathematical Models for Blood Flow and Coagulation Process

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Abstract. In this paper we introduce the key properties of blood flow and the blood coagulation process which are essential for their mathematical modelling. After this introduction we review possible approaches to the modelling of blood flow. The conditions of blood flow determine the blood coagulation process because blood flow carries chemical reactants to the area of coagulation. We will introduce the single continuum model of blood of Anand [2005] and its use in his modelling of blood coagulation. Then we present possibilities of mixture theory applications in the work of Jung et al. [2006], Massoudi and Antaki [2008], Málek and Rajagopal [2008]. We show the advantages of mixture theory models over single continuum models in the case of blood flow. We also compare classical and modern constitutive modelling and we show the advantages of the latter.

Introduction

Blood coagulation is a phenomenon whose physiological function is to prevent blood losses due to injury to vessel wall. Blood coagulation can also occur because of some pathological diseases such as arteriosclerosis, one of the lifestyle diseases. In such situations the coagulation is initiated without vessel wall injury. Blood coagulation can also occur on the surface of medical devices, which can be very unwelcome. Thus better understanding of the coagulation process could help us to improve the quality and length of contemporary human life.

Whole blood consists mainly of plasma, red blood cells (RBCs) or erythrocytes, white blood cells or leukocytes and platelets or thrombocytes. Over one half of the volume of total blood consists of plasma. RBCs make up 40–45% volume of blood; this value is called haematocrit. Blood plasma behaves as a Newtonian fluid with low apparent viscosity. In the following we will use terms viscosity and apparent viscosity interchangeably. Under normal conditions in the circulatory system RBCs determine the properties of whole blood. They are 6–8 μm in diameter and 2 μm thick discoid shaped cells, which have an elastic membrane on the surface and which are filled with haemoglobin. These features enable them to change shape easily. Under low shear rate flow conditions RBCs form column-like structures called rouleaux, which cause an increase in viscosity. These structures break up as shear rate increases. As RBCs have very strong influence on whole blood, the viscosity of blood has shear-thinning character. Due to the elasticity of RBCs, blood stores mechanical energy, which leads to viscoelastic behaviour of whole blood, as Thurston [1972] firstly recognized. Therefore blood behaves as viscoelastic fluid in small veins, where RBC deforms and stores elastic energy, while in larger arteries blood can be taken as a Newtonian fluid with shear-thinning viscosity. It is known from experiments (see Aarts et al. [1988]) that red blood cells stack around the middle of the vessel, pushing the platelets away from the centre of the vessel. Platelets are then concentrated mainly at the walls.

Blood coagulation begins under vessel injury conditions by the activation of blood platelets. This is caused by exposition of specific chemicals in the endothelium of the vessel wall. Blood platelets can also be activated by a prolonged exposure to a high or rapid increase in shear stress that leads to erythrocytes and platelets damage (see Hathcock [2006]). The exposition of the chemical in the endothelium triggers the so called coagulation cascade (see Figure 1), which is a complex set of enzymatic reactions with both positive and negative feedbacks (see Colman [2006]). Each reaction is characterised by a conversion of a proenzyme, zymogen, which is a non-active precursor of an enzyme, to an active enzyme. This activated enzyme then enables subsequent reactions proenzyme-enzyme in the cascade. The whole complex of reactions ends with the transformation of fibrinogen to fibrin. Fibrin strands then link together with the activated platelets in order to form the final cross-linked fibrin clot.

Most blood coagulation models have concentrated either on biochemistry of the process or rheology of blood flow. Combination of the two approaches is necessary in order to realistically describe blood coagulation process.
Existing single continuum models of blood coagulation

Quite a recent model of blood coagulation is presented in the work of Anand [2005]. In this model blood is captured as shear-thinning viscoelastic fluid which contains reactants of coagulation. It is supposed that these reactants do not affect the velocity field in either blood or clot. Blood clot is represented as highly viscoelastic fluid, in which reactants of clotting reactions are also present. Constitutive equations for whole blood and blood clot are gained by procedure of maximisation of rate of entropy production. This theoretical approach will be discussed later.

One of the key actors of blood coagulation, blood platelets, are activated by exposition to thrombin and adenosine diphosphate or by longer exposition to high values of shear stress. The coagulation cascade starts by exposition of tissue factor VIIa in the wall, i.e. if a certain value of concentration of this tissue factor is reached. It triggers the coagulation cascade, which ends with the creation of fibrin strands. Critical value of fibrin concentration marks then the area of clot in the flow. Fibrinolysis occurs either when concentration of fibrin falls under some critical value or some critical value of shear stress is reached. This value depends on the concentration of fibrin and blood platelets.

Let us now turn to the manner, the chemistry is captured in Anand’s model. The transport, activation and inhibition of reactants of blood coagulation is modelled by convection-diffusion-reaction equations

$$\frac{\partial [Y_i]}{\partial t} + \text{div}([Y_i]v) = \text{div}(D_{Y_i}\nabla[Y_i]) + G_{Y_i}, \quad i = 1..25,$$

where $[Y_i]$ stands for concentration of reactant $Y_i$, $G_{Y_i}$ represents creation and removal of reactant $Y_i$ due to enzymatic reactions (this term can depend on concentration of other reactants, the whole system of 25 equations is therefore coupled), $D_{Y_i}$ is diffusion coefficient of reactant $Y_i$, and $v$ is the velocity field either in blood or blood clot. It is supposed that the reactants do not have direct effect on the velocity distribution.

There are 25 reactants in the work of Anand. Bodnar and Sequeira [2008] implemented practical computation of this system of biochemical reactions under simplified rheological conditions. They assumed generalized Newtonian fluid for blood with shear-thinning viscosity. Blood clot was treated as an area with 100 times higher viscosity than that of blood. This area was determined by tracking fibrin concentration values in the whole computational area.

Existing application of mixture theory to blood flow

In the introduction we said that blood components are often distributed nonuniformly, especially blood platelets and erythrocytes. In the article of Jung et al. [2006] it is argued that single continuum models do not predict stacking of RBCs on the inside of curved arteries, where lower values of wall shear rate are present. One of the methods how to treat multicomponent suspension, such as blood, is mixture theory, which will be introduced in the following section.
Jung et al. [2006] treated blood as two-component mixture of plasma and RBCs. Plasma behaves like Newtonian fluid, RBCs have features of shear-thinning fluid. Momentum equation for component \( k = 1, 2 \) of this mixture is given as

\[
\frac{\partial (\rho_k \phi_k \mathbf{v}_k)}{\partial t} + \nabla \cdot (\rho_k \phi_k \mathbf{v}_k) = \phi_k \rho_k \mathbf{g} - \phi_k \nabla p + \nabla \cdot \phi_k \mathbf{T}_k + \sum_{l \neq k} \beta_{kl} (\mathbf{v}_k - \mathbf{v}_l) + \mathbf{F}_k,
\]

\( \rho_k, \phi_k \) is density of constituent \( k \), resp. volume fraction of constituent \( k \), \( \mathbf{g} \) is gravity force density, \( \mathbf{F}_k \) are external forces such as electricity and magnetism, \( \mathbf{v}_k \) is velocity of constituent \( k \), \( p \) is pressure, \( \mathbf{v}_l \) represents velocity of the other component of mixture \( l \neq k \), the stress tensors for each component \( k \) of the mixture are given

\[
\mathbf{T}_k = 2 \mu_k \mathbf{D}_k - \frac{2}{3} \mu_k \text{tr}(\mathbf{D}_k) \mathbf{1},
\]

where \( \mathbf{D}_k \) is the deformation tensor of component \( k \), \( \mu_k \) is the viscosity of component \( k \). Jung supplies also formulas for \( \beta_{kl} \), the interphase momentum exchange coefficients, which are reflecting the drag phenomenon in the mixture. The viscosity of red blood cell part of the mixture can be obtained from the relative shear-thinning viscosity relation for the whole blood

\[
\eta = \frac{\phi_{RBC} \mu_{RBC} + \phi_{plasma} \mu_{plasma}}{\mu_{plasma}} = m [1 + (\lambda \gamma^2)]^\frac{1}{2},
\]

where \( \mu_{plasma} \) is constant since plasma is treated as a Newtonian fluid, \( m, n \) are parameters, functions of haematocrit (\( \phi_{RBC} \)), \( \gamma \) is the shear rate, \( \lambda \) is material constant.

Numerical simulations based on Jung’s model capture quite good distribution of RBCs and plasma in the artery. The computations predicted higher concentration of RBCs at the places of lower wall shear rate, on the inside of curved arteries.

Alternative way of blood modelling in the framework of mixture theory was taken by Massoudi and Antaki [2008], who developed a model, where plasma is a Newtonian fluid and RBCs are solid particles. They assumed form of stress tensor for RBCs (for details see Massoudi [2005]):

\[
\mathbf{T} = \mathbf{T}(\rho, \nabla \rho, \mathbf{v}, \nabla \mathbf{v}, \mathbf{n}),
\]

where \( \rho \) is the bulk density of mixture, \( \mathbf{v} \) is velocity field identical with velocity field of plasma, \( \mathbf{n} \) represents the orientation of the RBC. Due to the requirement of frame-indifference the following constitutive equation was derived:

\[
\mathbf{T} = a_1 \mathbf{1} + a_2 \mathbf{m} \otimes \mathbf{m} + a_3 \mathbf{n} \otimes \mathbf{n} + a_4 (\mathbf{m} \otimes \mathbf{n} + \mathbf{n} \otimes \mathbf{m}) + a_5 \mathbf{D}
\]

\[
+ a_6 \mathbf{D}^2 + a_7 (\mathbf{m} \otimes \mathbf{D} \mathbf{m} + \mathbf{D} \mathbf{m} \otimes \mathbf{m})
\]

\[
+ a_8 (\mathbf{m} \otimes \mathbf{D}^2 \mathbf{m} + \mathbf{D}^2 \mathbf{m} \otimes \mathbf{m}) \mathbf{m}
\]

\[
+ a_9 (\mathbf{m} \otimes \mathbf{D} \mathbf{n} + \mathbf{D} \mathbf{n} \otimes \mathbf{n}) + a_{10} (\mathbf{n} \otimes \mathbf{D}^2 \mathbf{n} + \mathbf{D}^2 \mathbf{n} \otimes \mathbf{n})
\]

\[
+ a_{11} [(\mathbf{m} \otimes \mathbf{D} \mathbf{n} + \mathbf{D} \mathbf{n} \otimes \mathbf{m}) - (\mathbf{n} \otimes \mathbf{D} \mathbf{m} + \mathbf{D} \mathbf{m} \otimes \mathbf{n})]
\]

where \( \mathbf{m} = \nabla \rho \) and \( a_1, a_{11} \) are scalar functions of the set of invariants, including invariants of tensor \( \mathbf{D} \), which are for example listed in Massoudi and Antaki [2008], p.16. Under restriction to spherical particles, where anisotropy does not play a role, we get

\[
\mathbf{T} = b_1 \mathbf{1} + b_2 \mathbf{m} \otimes \mathbf{m} + b_3 \mathbf{D} + b_4 \mathbf{D}^2,
\]

where \( b_1, b_4 \) are scalar functions of appropriate invariants. Let us furthermore assume

\[
b_1 = \beta_0(\rho) + \beta_1(\rho) \mathbf{m} \cdot \mathbf{m} + \beta_2(\rho) \text{tr} \mathbf{D}, \quad b_2 = b_2(\rho), \quad b_3 = b_3(\rho), \quad b_4 = b_4(\rho),
\]

where \( \beta_0, \beta_1, \beta_2, b_2, b_3, b_4 \) are taken as functions of \( \rho \) only. Then, if we assume, that the effects of volume fraction gradient are negligible, implying that

\[
\beta_1 = b_2 = 0,
\]

then we get following form of stress tensor for RBCs:

\[
\mathbf{T} = [\tilde{\beta}_0(\phi) + \tilde{\beta}_2(\phi) \text{tr} \mathbf{D}] \mathbf{1} + \tilde{\beta}_3(\phi) \mathbf{D} + \tilde{\beta}_5(\phi) \mathbf{D}^2;
\]
where φ is the volume fraction of RBCs, haematocrit. For details of derivation see Massoudi and Antaki [2008]. Transition from βi(ρ), β2(ρ), b3(ρ) and b4(ρ) to βi(φ), β2(φ), b3(φ) and β5(φ) is not mere renaming, because bulk density ρ and volume fraction of RBCs φ (haematocrit) are different quantities.

In order to account for shear-thinning effects, viscosity coefficient β3 should depend on |D|^2

\[ β_3(φ, trD) = c(φ + φ^2)(|D|^2)^{1/2}. \quad (11) \]

If r < 0, then material is shear-thinning, c > 0 is constant. This type of constitutive modelling can be called classical. Its disadvantage is the dependence of constitutive relations on the material coefficients, which do not have clear physical interpretation. This feature is the most visible in the equation (6), where only coefficients α1, resp. α5, can be interpreted as pressure, resp. viscosity.

### Union of mixture theory with maximisation of rate of production of entropy framework

The classical constitutive modelling begins with supposition on tensor quantity, which is then subjected to restrictions of material frame indifference, isotropy, symmetry and second law of thermodynamics. Rajagopal and Srinivasa question this approach in Rajagopal and Srinivasa [2004], because the gained form of constitutive relations should, according to classical theory, be valid for arbitrary processes, which body could undergo. According to Málek and Rajagopal [2008] it is better to choose constitutive equations, which automatically meet the second law of thermodynamics and which are restricted to some specific class of processes.

Such a class of processes is determined by nonstandard part of non-equilibrium thermodynamical principle of maximisation of rate of entropy production. Relevance of this principle is questionable, elaborate discussion could be found in Martyushev and Seleznev [2006]. Rajagopal and Srinivasa in Rajagopal and Srinivasa [2004] argue that the use of such a principle in procedure outlined below is reasonable because it gives physically meaningful results in an array of various dissipative processes. Martyushev and Seleznev [2006] defends the principle on similar grounds.

We will show a sketch of the procedure in the case of mixture of two liquids. We will suppose specific form for the Helmholtz potential ψ and the rate of dissipation ξ. Superscripts in brackets denote quantities respective to one of the constituents of the mixture. Quantities without superscripts denote properties of the whole mixture. Since we ignore thermal effects and as we are dealing with a mixture of two fluids we shall assume that

\[ ψ = ψ(ρ^{(1)}, ρ^{(2)}) = Ψ(ρ). \quad (12) \]

The rate of dissipation consists of two parts. The first part is similar to the form of rate of dissipation of a single constituent compressible Navier-Stokes fluid. The second part corresponds to the frictional effects (drag) as one fluid is diffusing through the other:

\[ ξ = 2μ(ρ)|D|^2 + λ(ρ)(tr D)^2 + α(ρ)|v^{(1)} - v^{(2)}|^2, \quad (13) \]

where μ, resp. λ, is the first, resp. the second coefficient of viscosity, α is the drag coefficient. This three coefficients depend all on density of the mixture ρ. If we introduce the deviatoric part of the tensor A, i.e. \( A^d = A - \frac{1}{3}(tr A)1 \), then

\[ ξ = 2μ(ρ)|D|^2 + \left( \frac{2μ(ρ)}{3} + λ(ρ) \right)(tr D)^2 + α(ρ)|v^{(1)} - v^{(2)}|^2. \quad (14) \]

From the equation of continuity for mixture and the form of Helmholtz potential (12) it follows

\[ \frac{dΨ(ρ)}{dt} = -ρ^2Ψ'(ρ) tr D = -ρ^2Ψ'(ρ) div v, \quad (15) \]

where the prime denotes differentiation with respect to the density. Simplified form of the entropy production is

\[ \sum_{i=1}^{2} [T^{(i)}]^d \cdot [L^{(i)}]^d + \frac{1}{3} \sum_{i=1}^{2} tr T^{(i)} div v^{(i)} + ρ^2Ψ'(ρ) div v + m^{(1)} \cdot (v^{(2)} - v^{(1)}) = ξ, \quad (16) \]

where \( L^{(i)} = \nabla v^{(i)} \) is the velocity gradient associated with ith constituent, \( m^{(1)} \) is the interaction force acting on the first constituent due to the other constituent. This equation can be, with use of continuity
contain the material coefficients $\mu$. For detailed derivation see Málek and Rajagopal [2008]. We can see that constitutive relations (25–28) up to now we have prescribed equations for two scalar quantities: the Helmholtz potential $\psi$ of entropy production together with constraint (17).

We assume that the function $\lambda$, which is to be maximised, can depend on the following quantities

$$\xi = \xi \left( [L^{(1)}]^d, [L^{(2)}]^d, \text{div} \mathbf{v}^{(1)}, \text{div} \mathbf{v}^{(2)}, \mathbf{v}^{(2)} - \mathbf{v}^{(1)} \right).$$

The Lagrange function related to this problem

$$L = L \left( [L^{(1)}]^d, [L^{(2)}]^d, \text{div} \mathbf{v}^{(1)}, \text{div} \mathbf{v}^{(2)}, \mathbf{v}^{(2)} - \mathbf{v}^{(1)} \right)$$

is defined by

$$L = \xi + l[\xi - \sum_i [T^{(i)}]^d \cdot [L^{(i)}]^d - \sum_i \left( \frac{1}{3} \text{tr} T^{(i)} + \rho^{(i)} \rho \psi^{(i)}(\rho) \right) \text{div} \mathbf{v}^{(i)} - (m^{(1)} + \psi^{(i)}(\rho) r^{(12)}) \cdot (\mathbf{v}^{(2)} - \mathbf{v}^{(1)})],$$

where equation (17) is taken as constraint and $l$ is the corresponding Lagrange multiplier. We finally obtain following constitutive equations

$$T^{(1)} = -\rho^{(1)} \rho \psi^{(1)} \mathbf{1} + \left( \frac{2 \mu(\rho)}{3} + \lambda(\rho) \right) \frac{\rho^{(1)}}{\rho} (\text{div} \mathbf{v}) \mathbf{1} + 2 \mu(\rho) \frac{\rho^{(1)}}{\rho} \mathbf{D}^d,$$

$$T^{(2)} = -\rho^{(2)} \rho \psi^{(2)} \mathbf{1} + \left( \frac{2 \mu(\rho)}{3} + \lambda(\rho) \right) \frac{\rho^{(2)}}{\rho} (\text{div} \mathbf{v}) \mathbf{1} + 2 \mu(\rho) \frac{\rho^{(2)}}{\rho} \mathbf{D}^d,$$

$$m^{(1)} = \left( \frac{2 \mu(\rho)}{3} + \lambda(\rho) \right) (\text{div} \mathbf{v}) - \psi^{(1)}(\rho) (\rho^{(1)} \nabla \rho^{(2)} - \rho^{(2)} \nabla \rho^{(1)})$$

$$+ \frac{2 \mu(\rho)}{\rho} \mathbf{D} (\rho^{(1)} \nabla \rho^{(2)} - \rho^{(2)} \nabla \rho^{(1)}) + \alpha(\rho)(\mathbf{v}^{(2)} - \mathbf{v}^{(1)}).$$

For detailed derivation see Málek and Rajagopal [2008]. We can see that constitutive relations (25–28) contain the material coefficients $\mu$, $\lambda$ and $\alpha$, which have clear physical interpretation. This is not the case of the mentioned classical constitutive modelling.

**Conclusion**

In this article we discussed the possibilities of modelling the blood coagulation process and blood flow. We reviewed single continuum model of Anand [2005]. Single continuum models have problems with capturing some properties of multicomponent fluids based on the referenced article Jung et al. [2006]. Therefore we studied mixture theory application to blood flow. We introduced Jung’s model [Jung et al., 2006], which is quite simple, because blood plasma is modelled as a Newtonian fluid with constant viscosity and RBCs are modelled as a non-Newtonian fluid with shear-thinning viscosity. We have considered the use of mixture theory framework of Massoudi and Antaki [2008], who derived anisotropic stress tensor.
for RBC component of mixture RBCs-plasma. They used the procedure of classical constitutive modelling, which has the disadvantage of obtaining complicated relations with material coefficients, whose physical interpretation is not clear.

This problem could be solved by the application of modern constitutive modelling elaborated by Rajagopal and Srinivasa [2000, 2004]. We presented the use of this framework for a mixture of two liquids, which was elaborated by Málek and Rajagopal [2008].

Up to now we modelled Navier-Stokes fluids. However RBCs possess viscoelastic behaviour, which is the main challenge for further work. We would like to formulate two component mixture of plasma and RBCs, where stress tensor for RBCs captures as good as possible non-Newtonian features of RBCs. Rajagopal and Srinivasa [2000, 2004] developed a framework for viscoelastic fluids, which could be used for such models. We propose possible extension of the model of Málek and Rajagopal [2008] so that RBCs will be modelled as viscoelastic part of mixture. Constitutive equations for RBCs could be derived by the maximisation of rate of entropy production procedure, developed by Rajagopal and Srinivasa [2000, 2004]. Solution of the governing equations of flow will give us convective velocity, which will be used for transport equations for separate chemical species. Knowledge of distribution of reactants will be essential for further computations related to the blood coagulation process.

The crucial question of the mixture theory is the specification of boundary conditions, since experiments usually provide us with only with boundary conditions of the whole mixture. The boundary conditions of each part of mixture, which should be also specified, are hard to determine on experimental grounds. The proper specification of boundary condition should be the subject of mathematical and thermodynamic analysis.

References


