On the Implementation of a Non-linear Viscoelastic Model into Coupled Blood Flow-biochemistry Model

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Keywords: Blood, Viscoelastic Model, Coagulation, Finite-volume, Runge-Kutta.

Abstract: This paper presents selected numerical results obtained using a macroscopic blood coagulation model coupled with a non-linear viscoelastic model for blood flow. The governing system is solved using a central finite-volume scheme employing an explicit Runge-Kutta time-integration. An artificial compressibility method is used to resolve the pressure. A non-linear TVD filter is applied for stabilization. A simple test case of blood flow over a clotting surface in a straight 3D vessel is solved. This work merges and significantly extends our previous studies (Bodnár and Sequeira, 2008) and (Bodnár et al., 2011a).

1 INTRODUCTION

Mathematical and numerical modeling of blood related phenomena is a very challenging problem.

The flow of blood is difficult to solve mainly due to its complex rheological behavior which can be highly non-Newtonian in certain flow regimes (Robertson et al., 2008; Robertson et al., 2007; Galdi et al., 2008). Phenomena like shear-thinning viscosity, viscoelasticity or thixotropy can be observed. Corresponding models for blood have been developed including several of these features. To date, there is no single, generally accepted rheological model for blood. The modeling is done on case to case basis depending on flow conditions and actual needs in predicting the blood behavior. The work presented here follows on previous studies (Bodnár and Sequeira, 2010; Bodnár et al., 2009; Bodnár et al., 2011b) describing the shear-thinning and viscoelastic behavior of blood in simple geometries. Even if the blood flow problem is considered as a purely mechanical phenomena, its mathematical modeling and numerical simulation is a subject of several serious challenges as demonstrated e.g. in (Janela et al., 2010; Gambaruto et al., 2011) or (Pirkl et al., 2011).

The rheology of blood as well as its flow is heavily affected by the underlying microstructure and is closely related to the biochemistry of reacting blood constituents. Blood coagulation has been recognized for a long time as one of the most complex problems in biology as described recently e.g. in (Fasano et al., 2012). There has been several blood coagulation models developed in the past based on different modeling strategies (Mann et al., 2006; Ataullakhanov et al., 2002; Zarnitsina et al., 1996; Butenas and Mann, 2002) or (Kuharsky and Fogelson, 2001; Anand et al., 2003). One of the major problems is the high complexity of the chemical system which crucially depends on the supply of chemicals by the flow. This leads to an important dependence of the coagulation process on the blood flow. On the other hand the flow is determined by the extent of the clot, forming an obstacle to blood flow.

This is why any future successful model of blood coagulation necessarily has to be coupled with the blood flow. The blood itself exhibits a very complicated rheological behavior including phenomena such as viscoelasticity and shear-thinning. The aim of this paper is to present a successful way of coupling two of the most complex macroscopic continuum based models of blood flow and biochemistry proposed in (Anand et al., 2003; Anand et al., 2008). The work presented herein merges and significantly extends our previous studies (Bodnár and Sequeira, 2008) and (Bodnár et al., 2011a). Due to the lack of space here, we refer the reader to these papers for many details concerning the model development and implementation as these are necessary to fully under-

Bodnár T. and Sequeira A..
On the Implementation of a Non-linear Viscoelastic Model into Coupled Blood Flow-biochemistry Model.
DOI: 10.5220/0004621306520657
In *Proceedings of the 3rd International Conference on Simulation and Modeling Methodologies, Technologies and Applications* (BIOMED-2013), pages 652-657
ISBN: 978-989-8565-69-3

stand the work presented below.

2 MATHEMATICAL MODELS

The mathematical model consists of several parts describing the flow of blood and a biochemical cascade leading to clot formation.

2.1 Blood Flow Model

The flow is described by a non-linear shear-thinning viscoelastic model following the thermodynamic framework established in (Rajagopal and Srinivasa, 2000) and extended for blood flow in (Anand and Rajagopal, 2004). The set of governing equations is based on the conservation of mass (reduced to divergence-free constraint) and conservation of linear momentum for an incompressible fluid.

$$\operatorname{div} \boldsymbol{u} = 0. \quad (1)$$

$$\rho \frac{D\boldsymbol{u}}{Dt} = \operatorname{div} \boldsymbol{T} \quad (2)$$

The stress tensor $\boldsymbol{T}$ is split as follows:

$$\boldsymbol{T} = -p\mathbf{1} + \mu \boldsymbol{B}_{\kappa_p(t)} + \eta_1 \boldsymbol{D} \quad (3)$$

where $\boldsymbol{D}$ denotes the symmetric part of the velocity gradient tensor and $\mathbf{1}$ stands for identity tensor. The upper-convected time-derivative of the elastic stretch tensor $\boldsymbol{B}_{\kappa_p(t)}$ is given by[1]:

$$\overset{\triangledown}{\boldsymbol{B}}_{\kappa_p(t)} = -2K \left(\operatorname{tr}(\boldsymbol{B}_{\kappa_p(t)}) - 3\lambda \right)^n \left[\boldsymbol{B}_{\kappa_p(t)} - \lambda \mathbf{1} \right] \quad (4)$$

where the coefficient λ depends on the trace of the inverse of the tensor $\boldsymbol{B}_{\kappa_p(t)}$ according to

$$\lambda = \frac{3}{\operatorname{tr}\left(\boldsymbol{B}^{-1}_{\kappa_p(t)} \right)} \quad . \quad (5)$$

The remaining model coefficients for blood are taken exactly from (Anand and Rajagopal, 2004):

$$\eta_1 = 0.01\, Pa \cdot s \qquad \mu = 0.1611\, N/m^2$$

$$n = 0.5859 \qquad K = 58.0725\, s^{-1}$$

More details and explanation concerning this model and its implementation can be found e.g. in our previous paper (Bodnár et al., 2011a).

[1]The subscript $\kappa_p(t)$ is used to emphasize that the stretch is expressed with respect to natural (time dependent) configuration $\kappa_p(t)$. This notation follows exactly the original papers (Rajagopal and Srinivasa, 2000; Anand and Rajagopal, 2004) and (Bodnár et al., 2011a) where the model has been introduced and used.

2.2 Biochemistry Model

The biochemistry model is based on a coupled set of advection-diffusion-reaction (ADR) equations. It has been originally developed in (Anand et al., 2003) and further extended in (Anand et al., 2008). It describes the spatio-temporal evolution of concentrations C_i of 23 chemical constituents (enzymes, zymogens, proteins, etc.).

$$\frac{DC_i}{Dt} = \operatorname{div}(K_i \operatorname{grad} C_i) + R_i \quad (6)$$

The non-linear chemical reaction terms R_i are mainly based on second order or Michaelis-Menten kinetics. As an example let's mention the reaction term R_{Ia} in the equation for fibrin[2]:

$$R_{Ia} = \frac{k_1 [IIa][I]}{K_{1M} + [I]} - \frac{h_1 [PLA][Ia]}{H_{1M} + [Ia]} \quad (7)$$

The concentrations of *thrombin* (denoted by $[IIa]$), *fibrinogen* (denoted by $[I]$), *fibrin* (denoted by $[Ia]$) and *plasminogen* (denoted by $[PLA]$) are used to evaluate the reaction term R_{Ia}. The chemical kinetics rates k_1, h_1 and constants K_{1M}, H_{1M} are known (taken from (Anand et al., 2008)). The values of the diffusion parameters K_i and the exact form of the reaction terms R_i are given in (Bodnár and Sequeira, 2008), where the model has been for the first time implemented and used in 3D simulations.

2.3 Coupling Strategy

The coupling between blood flow and biochemistry is based on the fibrin concentration. *Fibrin* is one of the major constituents of clots (Fasano et al., 2012) and thus it can be used as an indicator of the clot formation. The main idea is to make the material properties of blood/clot dependent on fibrin concentration. For low fibrin concentration the fluid behaves like blood, while for high fibrin concentration it changes its behavior to a clot-like medium. In our model the fluid viscosity is multiplied by a factor $\tilde{\eta}_1$ that locally depends (linearly, up to a certain saturation value η^*) on fibrin concentration $[Ia]$. The viscosity η_1 is multiplied by a non-dimensional factor $\tilde{\eta}_1$

$$\tilde{\eta}_1 = \min\left\{ 1 + \frac{\eta^* - 1}{C_{clot}} [Ia], \eta^* \right\} \quad (8)$$

In our study we have used $\eta^* = 100$ and $C_{clot} = 1000\ nM$.

The clot is thus characterized as a highly viscous fluid. As a result, the region occupied by this simulated clot represents an obstacle to the flow of blood,

[2]The subscript *Ia* refers to the chemical notation for fibrin.

with much lower viscosity. This effect is even significantly magnified due to the shear-thinning non-Newtonian behavior of blood, leading to a further increase of fluid viscosity in regions of low shear.

Changes in viscosity modify the local flow field which consequently affects the concentration field that leads to further changes in viscosity. In this way the two-way biochemistry-flow coupling is enforced.

More details on this simple coupling technique can be found in (Bodnár and Sequeira, 2008) where it has been used together with a generalized Newtonian model for blood, i.e. neglecting the viscoelasticity. In the present study the technique has been extended to the new non-linear viscoelastic model as suggested in (Anand and Rajagopal, 2002; Anand et al., 2005; Anand et al., 2008).

3 NUMERICAL METHODS

The system of governing equations is rather complex and highly non-linear. This is why the numerical discretization has been chosen to be as simple and predictable as possible. We do not claim this choice is optimal, it only serves as the first step that allows us to evaluate the underlying mathematical model and test its applicability in simple configurations. The semi-discretization approach is adopted to first discretize the PDEs in space and then integrating the resulting system of ODEs in time. The same discretization is employed for flow variables, viscoelastic stress tensor and concentrations in the biochemistry model.

The *space discretization* is based on a simple central finite-volume discretization on a structured grid with hexahedral cells. A multiblock grid topology with wall-fitted cells was used. The viscous fluxes are also discretized by the finite-volume technique over a diamond-shaped cells adjoint to primary control volumes faces. This approach was used in our previous papers (Bodnár and Příhoda, 2006; Bodnár and Sequeira, 2010; Bodnár et al., 2011b) or in (Keslerová and Kozel, 2011; Keslerová, 2013).

The *time integration* is performed using a Runge-Kutta (RK) multistage scheme. A specific advection-diffusion optimized RK method has been used to reduce the computational cost. The basic idea behind this subclass of RK methods is to split the space-discretization operator into its inviscid and viscous part. The inviscid part is evaluated in every stage of RK method while the viscous fluxes are only evaluated in few stages. This corresponds to an operator splitting technique with different RK methods (coefficients) used for the advection step and another for the diffusion step. This approach allows to save several (very expensive) evaluations of diffusive fluxes per time-step, while retaining the rather large stability region of the RK method. For details see (Jameson et al., 1981; Jameson, 1991) or (Bodnár and Sequeira, 2010; Bodnár et al., 2011b).

Along with these two basic components of the numerical solver a specific stabilization technique is used to avoid non-physical numerical oscillations due to the central discretization. The non-linear TVD filter (Engquist et al., 1989; Shyy et al., 1992) was used to smooth the concentration fields, as reported recently in (Bodnár, 2012).

4 NUMERICAL RESULTS

The numerical test case follows almost exactly the setups used in (Bodnár and Sequeira, 2008) and (Bodnár et al., 2011a) where we refer the complete parameter set for this simulation. The geometry represents a straight section of a blood vessel with diameter $6.2\,mm$ and length $31\,mm$ with the grid shown in the figure 1. The clotting surface is simulated in a region

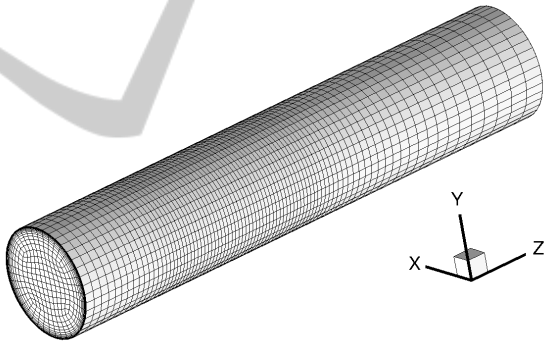

Figure 1: Grid structure.

that is formed by the intersection of a sphere with the blood vessel wall. The evolution in space and time of the clot is tracked down.

The model is very complex and thus the simulations generate large amounts of data to be visualized, analyzed, and understood. In this paper only a few snapshots of results are presented to demonstrate some of the most important types of model outputs.

The evolution in time of some of the coagulation factors can be seen in the figures 3, 2 and 4. The concentration is visualized in a single point located in the center of the clotting surface on the vessel wall. Only the initial 600 seconds of clotting are shown. These graphs show the nature of the coagulation process, initially very fast, with rather slow long term evolution in the later phase.

The spatial extent of the clot can be shown using

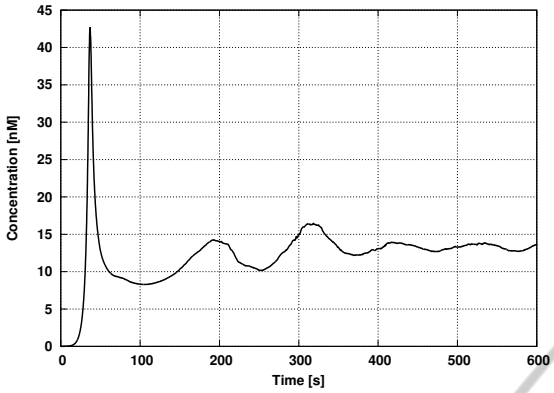

Figure 2: Thrombin (Factor IIa) concentration.

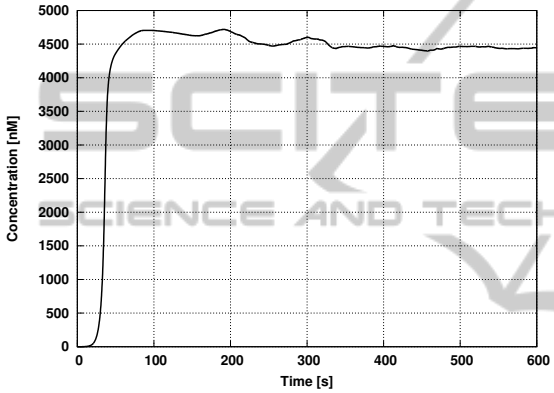

Figure 3: Fibrin (Factor Ia) concentration.

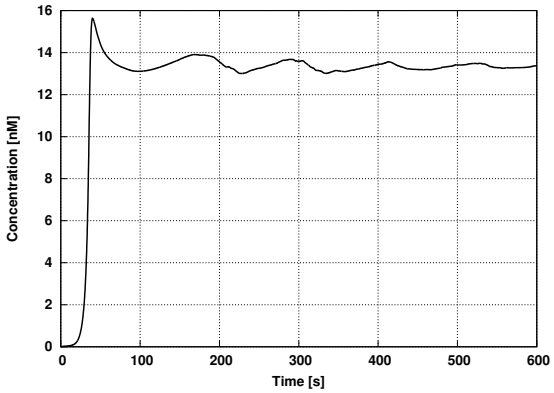

Figure 4: Tissue Plasminogen Activator (tPA) concentration.

the contours of fibrin. Figure 5 shows the contours of fibrin concentration on the surface of the blood vessel (in the range 50–5000nM in 15 levels with exponential distribution) and their variation in time. It is evident that the core of the clot is rather stable in time, while the downstream concentration field varies in time as a consequence of the interaction with the blood flow.

The flow field is modified in the clot region as depicted in figure 6, showing the contours of the axial velocity in the near-wall layer (the first grid cell). The red color means high velocity, while blue color is used in low speed regions. The flow is not only decelerated in the clotting area, but it is also deflected in the tangential direction as it is shown in figure 7. The green color is used in unaffected regions, while the red/blue is used for positive/negative values. This is only shown to demonstrate the qualitatively correct behavior of the flow, that is stopped inside the clotting area and forced to flow around this region. The exact contour values are not given as they depend on the distance from the wall which was chosen arbitrarily just for illustration.

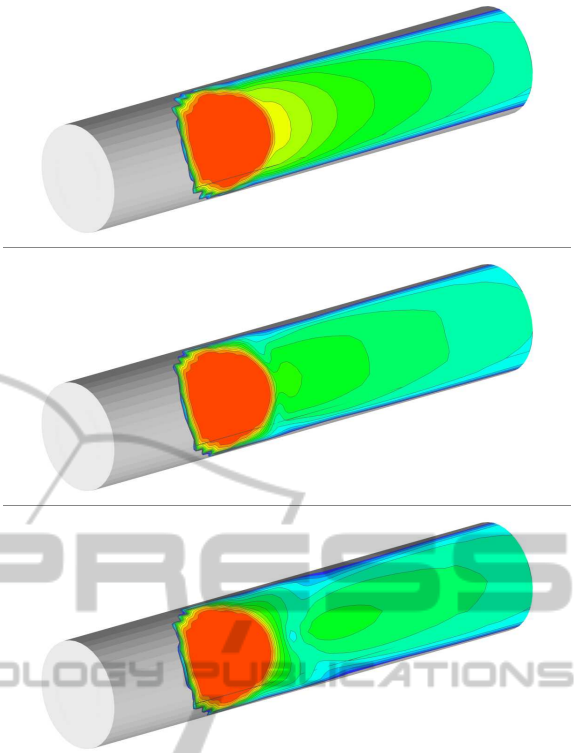

Figure 5: Fibrin concentration evolution (Time=200*s*,400*s*,600*s*).

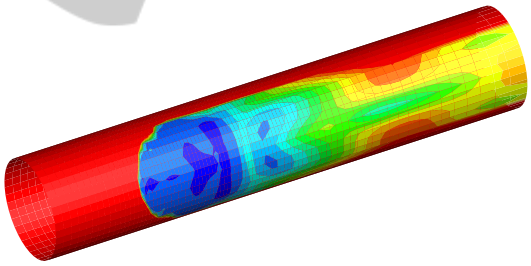

Figure 6: Axial velocity in near-wall layer.

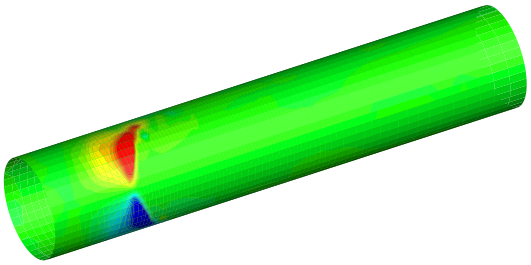

Figure 7: Tangential velocity in near-wall layer.

5 CONCLUSIONS

The numerical study presented in this paper has demonstrated the successful implementation of both, the blood flow and the biochemistry model. The model is now more complex in comparison with the one presented in our previous work on blood coagulation (Bodnár and Sequeira, 2008). The viscoelastic extension of the model should allow to extend the range of applicability of the model to critical flow regimes. The price to pay for this non-linear viscoelastic model extension is an important increase of computational cost. The original, generalized Newtonian model with shear-thinning viscosity, contained $4+23=27$ PDEs to solve in 3D. The new model has 6 more equations for the components of the viscoelastic stress tensor. This means that we have to solve now $4+6+23=33$ equations for the coupled flow + rheology + biochemistry model.

Future research will focus on performance and robustness improvements of the model and numerical solvers. The stability issues raised in (Sequeira et al., 2011) should be also addressed in the context of this new model. Both of these topics will be important in future applications of the model requiring long time clot evolution simulations.

ACKNOWLEDGEMENTS

The financial support for the present project was partly provided by the *Czech Science Foundation* under the *Grant No.201/09/0917* and by the *Portuguese Science Foundation* under the *Project EXCL/MAT-NAN/0114/2012*.

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