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Numerical Simulation of Viscoelastic Fluid-Structure Interaction Problems and Drug Therapy in the Eye

Alexander Drobny[1,*] and **Elfriede Friedmann**[1,**]

[1] Institute of Mathematics, University of Kassel, Heinrich-Plett-Str. 40, 34132 Kassel, Germany

The vitreous is a fluid-like viscoelastic transparent medium located in the center of the human eye and is surrounded by hyperelastic structures like the sclera, lens and iris. This naturally gives rise to a fluid-structure interaction (FSI) problem. While the healthy vitreous is viscoelastic and described by a viscoelastic Burgers-type equation, the aging vitreous liquefies and is therefore modeled by the Navier-Stokes equations. We derive a monolithic variational formulation employing the arbitrary Lagrangian Eulerian framework which is solved using the finite element method. To allow large 3D simulations the implementation is parallelized. Furthermore we study the vascular endothelial growth factor (VEGF) therapy in the vitreous which is modeled by four coupled convection-diffusion-reaction equations with an additional coupling to the underlying flow.

1 Introduction

In this work we perform three dimensional finite element simulations of viscoelastic FSI problems in the eye and of a drug therapy model in the vitreous based on four coupled convection-diffusion-reaction equations.

2 Variational Formulations

The variational formulation for the viscoelastic FSI models (see [1] for details on the models and parameters) employing the arbitrary Lagrangian Eulerian (ALE) framework [2] using appropriate function spaces reads:

Definition 2.1 Find $\{\hat{v}_f, \hat{v}_s, \hat{u}_f, \hat{u}_s, \hat{p}_f, \hat{B}_1, \hat{B}_2\} \in \{\hat{v}_f^D + \hat{V}_{f,\hat{v}}^0\} \times \hat{L}_s \times \{\hat{u}_f^D + \hat{V}_{f,\hat{u}}^0\} \times \{\hat{u}_s^D + \hat{V}_s^0\} \times \hat{L}_f^0 \times \hat{V}_f \times \hat{V}_f$ such that $\hat{v}_f(0) = \hat{v}_f^0$, $\hat{v}_s(0) = \hat{v}_s^0$, $\hat{u}_f(0) = \hat{u}_f^0$, $\hat{u}_s(0) = \hat{u}_s^0$, $\hat{B}_1(0) = I$, $\hat{B}_2(0) = I$ and for almost all time steps $t \in I$ it holds:

$$
\begin{aligned}
(\hat{J}\hat{\rho}_f \partial_t \hat{v}_f, \hat{\psi}^v)_{\hat{\Omega}_f} + (\hat{\rho}_f \hat{J}(\hat{F}^{-1}(\hat{v}_f - \partial_t \hat{u}_f)\cdot\hat{\nabla})\hat{v}_f, \hat{\psi}^v)_{\hat{\Omega}_f} + (\hat{J}\hat{\sigma}_f \hat{F}^{-T}, \hat{\nabla}\hat{\psi}^v)_{\hat{\Omega}_f} - (\hat{\rho}_f \hat{J}\hat{f}_f, \hat{\psi}^v)_{\hat{\Omega}_f} &= 0 \; \forall \hat{\psi}^v \in \hat{V}_{f,\hat{\Gamma}_i}^0, \\
(\hat{J}(\partial_t \hat{B}_1 + (\hat{\nabla}\hat{B}_1)(\hat{F}^{-1}(\hat{v}_f - \partial_t \hat{u}_f)) - (\hat{\nabla}\hat{v}_f)\hat{F}^{-1}\hat{B}_1 - \hat{B}_1\hat{F}^{-T}(\hat{\nabla}\hat{v}_f)^T + \frac{\mu_1}{\nu_1}(\hat{B}_1 - I)), \hat{\psi}^{B_1})_{\hat{\Omega}_f} &= 0 \; \forall \hat{\psi}^{B_1} \in \hat{V}_f, \\
(\hat{J}(\partial_t \hat{B}_2 + (\hat{\nabla}\hat{B}_2)(\hat{F}^{-1}(\hat{v}_f - \partial_t \hat{u}_f)) - (\hat{\nabla}\hat{v}_f)\hat{F}^{-1}\hat{B}_2 - \hat{B}_2\hat{F}^{-T}(\hat{\nabla}\hat{v}_f)^T + \frac{\mu_2}{\nu_2}(\hat{B}_2 - I)), \hat{\psi}^{B_2})_{\hat{\Omega}_f} &= 0 \; \forall \hat{\psi}^{B_2} \in \hat{V}_f, \\
(\hat{\rho}_s \partial_t \hat{v}_s, \hat{\psi}^v)_{\hat{\Omega}_s} + (\hat{\Pi}, \hat{\nabla}\hat{\psi}^v)_{\hat{\Omega}_s} - (\hat{\rho}\hat{f}_s, \hat{\psi}^v)_{\hat{\Omega}_s} &= 0 \; \forall \hat{\psi}^v \in \hat{V}_s^0, \\
\hat{\rho}_s(\partial_t \hat{u}_s - \hat{v}_s, \hat{\psi}^u)_{\hat{\Omega}_s} &= 0 \; \forall \hat{\psi}^u \in \hat{L}_s, \\
(\widehat{\mathrm{div}}(\hat{J}\hat{F}^{-1}\hat{v}_f), \hat{\psi}^p)_{\hat{\Omega}_f} &= 0 \; \forall \hat{\psi}^p \in \hat{L}_f^0, \\
(\alpha\hat{\nabla}\hat{u}_f, \hat{\nabla}\hat{\psi}^u)_{\hat{\Omega}_f} &= 0 \; \forall \hat{\psi}^u \in \hat{V}_{f,\hat{u},\hat{\Gamma}_i}^0
\end{aligned}
$$

with $\hat{\sigma}_f = -\hat{p}_f I + \hat{\rho}_f \nu_3(\hat{\nabla}\hat{v}_f\hat{F}^{-1} + \hat{F}^{-T}\hat{\nabla}\hat{v}_f^T) + \mu_1(\hat{B}_1 - I) + \mu_2(\hat{B}_2 - I)$, $\hat{\Pi} = \frac{\partial}{\partial \hat{F}}(\frac{1}{2}\mu(\hat{J}^{-2/3}\mathrm{tr}(\hat{F}^T\hat{F}) - 3) + \frac{1}{2}\kappa(\ln\hat{J})^2)$.

Here $\hat{v}$ is the velocity, $\hat{p}_f$ the pressure, $\hat{u}$ the displacement, $\hat{B}$ the viscoelastic tensors, $\hat{\rho}$ the densities, ν the viscosities, $\hat{\sigma}_f$ and $\hat{\Pi}$ the stress tensors, $\hat{J} = \det\hat{F}$, $\hat{F} = \hat{I} + \hat{\nabla}\hat{u}$. The subscript "f" and "s" denote the fluid and structure domains. In case of the Navier-Stokes equations the terms involving $\hat{B}_1$ and $\hat{B}_2$ drop. As mesh motion PDE we choose a standard harmonic extension. Fluid-structure interface conditions are continuity of velocity and displacement and balance of the normal stresses. For the structure-structure interface we require similar conditions. For details on the models see [1], [4] and [3].

The model for the drug therapy consists of four coupled convection-diffusion-reaction equations and the Burgers or Navier-Stokes equations as the underlying flow. The reaction terms and permeabilities of the boundaries are based on [5]. The concentration c_a is the drug which is injected into the vitreous. The goal for the medicine is to couple to the second concentration c_v (VEGF), reducing the amount of free VEGF in the vitreous. Due to the two binding sites of the VEGF we have two concentrations c_va and c_ava modeling the medicine-VEGF complex and medicine-VEGF-medicine complex. We define the following reaction terms $R_1(c_\mathrm{a}, c_\mathrm{v}, c_\mathrm{va}) = k_\mathrm{off}c_\mathrm{va} - 2k_\mathrm{on}c_\mathrm{v}c_\mathrm{a}$, $R_2(c_\mathrm{a}, c_\mathrm{va}, c_\mathrm{ava}) = 2k_\mathrm{off}c_\mathrm{ava} - k_\mathrm{on}c_\mathrm{a}c_\mathrm{va}$ for a more compact problem formulation. Using a similar notation to Definition 2.1 the variational formulation for the drug therapy model reads:

* Corresponding author: E-mail adrobny@mathematik.uni-kassel.de
** E-mail friedmann@mathematik.uni-kassel.de

Definition 2.2 Find $\{v, p, B_1, B_2, c_\mathrm{a}, c_\mathrm{v}, c_\mathrm{va}, c_\mathrm{ava}\} \in \{v^D + H_0^1(\Omega)\} \times L^2(\Omega) \times H^1(\Omega) \times H^1(\Omega) \times H^1(\Omega) \times H^1(\Omega) \times H^1(\Omega) \times H^1(\Omega)$ such that $v(0) = v^0$, $B_1(0) = I$, $B_2(0) = I$, $c_\mathrm{a}(0) = c_\mathrm{a}^0$, $c_\mathrm{v}(0) = c_\mathrm{v}^0$, $c_\mathrm{va}(0) = c_\mathrm{va}^0$, $c_\mathrm{ava}(0) = c_\mathrm{ava}^0$ and for almost all time steps $t \in I$ it holds:

$$
\begin{aligned}
\rho(\partial_t v, \psi^v)_\Omega + \rho(v \cdot \nabla v, \psi^v)_\Omega + (\sigma, \nabla \psi^v)_\Omega - \langle \sigma n, \psi^v \rangle_{\Gamma_N} - \rho(f, \psi^v)_\Omega &= 0 \; \forall \psi^v \in H_0^1(\Omega), \\
(\mathrm{div} v, \psi^p)_\Omega &= 0 \; \forall \psi^p \in L^2(\Omega), \\
(\partial_t B_1 + (\nabla B_1)v - (\nabla v)B_1 - B_1(\nabla v)^T + \frac{\mu_1}{\nu_1}(B_1 - I), \psi^{B_1})_\Omega &= 0 \; \forall \psi^{B_1} \in H^1(\Omega), \\
(\partial_t B_2 + (\nabla B_2)v - (\nabla v)B_2 - B_2(\nabla v)^T + \frac{\mu_2}{\nu_2}(B_2 - I), \psi^{B_2})_\Omega &= 0 \; \forall \psi^{B_2} \in H^1(\Omega), \\
(\partial_t c_\mathrm{a} + v \cdot \nabla c_\mathrm{a}, \psi^{c_\mathrm{a}}) + (D_\mathrm{a} \nabla c_\mathrm{a}, \nabla \psi^{c_\mathrm{a}}) - \langle D_\mathrm{a} \partial_n c_\mathrm{a}, \psi^{c_\mathrm{a}} \rangle_{\Gamma_N} - (R_1, \psi^{c_\mathrm{a}}) - (R_2, \psi^{c_\mathrm{a}}) &= 0 \; \forall \psi^{c_\mathrm{a}} \in H^1(\Omega), \\
(\partial_t c_\mathrm{v} + v \cdot \nabla c_\mathrm{v}, \psi^{c_\mathrm{v}}) + (D_\mathrm{v} \nabla c_\mathrm{v}, \nabla \psi^{c_\mathrm{v}}) - \langle D_\mathrm{v} \partial_n c_\mathrm{v}, \psi^{c_\mathrm{v}} \rangle_{\Gamma_N} - (R_1, \psi^{c_\mathrm{v}}) &= 0 \; \forall \psi^{c_\mathrm{v}} \in H^1(\Omega), \\
(\partial_t c_\mathrm{va} + v \cdot \nabla c_\mathrm{va}, \psi^{c_\mathrm{va}}) + (D_\mathrm{va} \nabla c_\mathrm{va}, \nabla \psi^{c_\mathrm{va}}) - \langle D_\mathrm{va} \partial_n c_\mathrm{va}, \psi^{c_\mathrm{va}} \rangle_{\Gamma_N} + (R_1, \psi^{c_\mathrm{va}}) - (R_2, \psi^{c_\mathrm{va}}) &= 0 \; \forall \psi^{c_\mathrm{va}} \in H^1(\Omega), \\
(\partial_t c_\mathrm{ava} + v \cdot \nabla c_\mathrm{ava}, \psi^{c_\mathrm{ava}}) + (D_\mathrm{ava} \nabla c_\mathrm{ava}, \nabla \psi^{c_\mathrm{ava}}) - \langle D_\mathrm{ava} \partial_n c_\mathrm{ava}, \psi^{c_\mathrm{ava}} \rangle_{\Gamma_N} + (R_2, \psi^{c_\mathrm{ava}}) &= 0 \; \forall \psi^{c_\mathrm{ava}} \in H^1(\Omega)
\end{aligned}
$$

with $\sigma = -pI + \rho\nu(\nabla v + \nabla v^T) + \mu_1(B_1 - I) + \mu_2(B_2 - I)$.

3 Numerical Results

The numerical simulations are realized in deal.ii [6] and based on the FSI implementation in [7]. We use Q_2 finite elements for the velocity, displacement, concentrations and viscoelastic tensors and discontinuous P_1^{dc} elements for the pressure. Temporal discretization is based on the backward Euler scheme. Figure 1 shows a FSI simulation in a simplified eye geometry (similar to experiments in [8]) where the eye is fixed on the left and pulled to the right. Figure 2 shows the cell-wise norm of the stress for a healthy and vitrectomized vitreous. In most areas the stress is higher for the healthy vitreous.

Figure 3 shows the mesh and the velocity of the flow for the drug therapy model. The blue area is the inflow area for the flow. The concentrations can leave through the blue and red areas. Figure 4 shows the concentrations of a slice through the vitreous after two days and the average concentration over time showing the VEGF reducing mechanism of the drug.

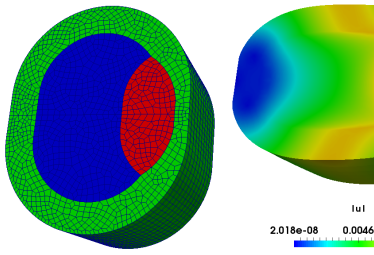

Fig. 1: left: The FSI mesh: blue: fluid domain, red/green elastic structures, right: $|u|$

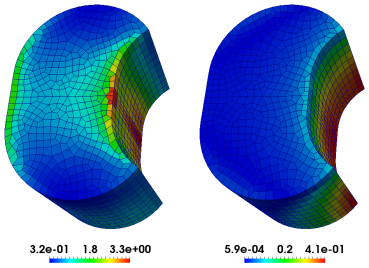

Fig. 2: l: healthy vitreous (Burgers), r: vitrectomized vitreous (Navier-Stokes)

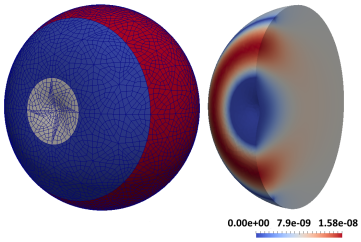

Fig. 3: l: The mesh for the drug model r: velocity in the vitreous cut in the middle

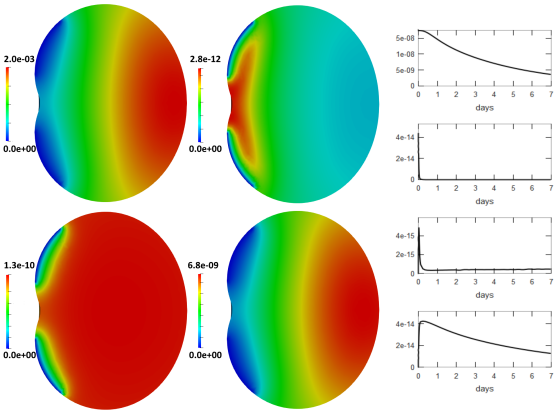

Fig. 4 Concentrations after two days: top left to bottom right: c_a, c_v, c_va, c_ava and the average concentration over time

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References

[1] A. Drobny and E. Friedmann, PAMM **19**(1), e201900348 (2019).
[2] J. Donea, S. Giuliani, and J. P. Halleux, Computer methods in applied mechanics and engineering **33**(1-3), 689–723 (1982).
[3] R. Grytz, M. A. Fazio, M. J. Girard, V. Libertiaux, L. Bruno, S. Gardiner, C. A. Girkin, and J. C. Downs, Journal of the mechanical behavior of biomedical materials **29**, 602–617 (2014).
[4] K. Tůma, J. Stein, V. Průša, and E. Friedmann, arXiv preprint arXiv:1802.04002 (2018).
[5] L. A. Hutton-Smith, E. A. Gaffney, H. M. Byrne, A. Caruso, P. K. Maini, and N. A. Mazer, Molecular pharmaceutics **15**(7), 2770–2784 (2018).
[6] W. Bangerth, R. Hartmann, and G. Kanschat, ACM Trans. Math. Softw. **33**(4), 24/1–24/27 (2007).
[7] T. Wick, Archive of Numerical Software **1**(1), 1–19 (2013).
[8] N. S. Shah, D. C. Beebe, S. P. Lake, and B. A. Filas, Annals of biomedical engineering **44**(10), 3084–3095 (2016).