Diploma thesis

Numerical simulation of platelet adhesion, activation and aggregation

Application to Taylor-Couette systems

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Abstract

Background: Heart attack and stroke are among the leading causes of death in industrial nations but the number of candidates needing a transplant exceeds the number of transplants performed. Due to this chronic shortage, blood pumps are needed to deliver appropriate hydraulic performance while maintaining physiological flow conditions. Because all known artificial materials are considered to be thrombogenic to some extent it is necessary to investigate the interaction of flow and material in complex geometries to optimize modern blood pumps and other artificial organs. As human blood is a precious fluid, designers of rotational blood pumps desire reliable predictive thrombosis models to optimize the physiological compatibility of their devices. In this thesis, the initial development stage of a model for platelet adhesion, activation and aggregation is described. Model equations and methods for their numerical solution are presented. The Taylor-Couette system, as a well investigated rotational device, is simulated as a test case to estimate model parameters and to explore the predictive accuracy of the model.

Results: Adhesion rates for polystyrene surfaces were obtained by fitting numerical simulations to experimental results for laminar flow. These parameters were used to simulate the effects on the platelets in Taylor vortex flow based on a pre-computed velocity field.

Conclusions: Without proper care, fitting can result in unphysiological model parameters. Numerical optimization methods can help finding better parameters, but cannot yet entirely replace parameter guessing. Platelet migration and other shear-dependent effects will have to be included in the model to reproduce the results in case of Taylor vortex flow.
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Chapter 1

Introduction

1.1 Motivation

Heart attack and stroke are among the leading causes of death in industrial nations. According to the World Health Organization (WHO), coronary heart disease (17.1 %) followed by stroke and other cerebrovascular diseases (9.8 %) were the most prevalent death causes in high-income countries in 2002 [59].

While heart transplantations do save thousands of lives per year, many patients suffer from heart diseases because the number of candidates needing a transplant exceeds the number of transplants performed. Due to this chronic shortage, artificial organs are needed to provide both, short and long term support, either as a bridge to transplantation (BTT), or in the future, even as a permanent replacement. Patients with remaining cardiac function can receive a ventricular assist device (VAD) that supports the heart. VADs need to be distinguished from total artificial hearts as they do not replace the heart but take over part of or even the entire heart’s function. In some cases, ventricular support even allows the heart to rest and recover up to the point that its function improves and the VAD can be removed without a heart transplant. The major component of both – artificial hearts and VADs – is a blood pump. The main function of a blood pump is to deliver appropriate hydraulic performance while maintaining physiological flow conditions. The contact of blood with foreign materials however leads to a notable activation of blood cells and plasma factors. Effects on the properties of blood in contact with bio-engineered materials depend to a large extent on the flow conditions that are investigated in the field of hemorheology. Another important objective in blood pump engineering is hemocompatibility, which characterizes the ability of a biomaterial in direct contact with blood to operate without inducing significant immune responses. Because all known artificial materials are considered to be thrombogenic to some extent – only endothelial cells are not thrombogenic – it is necessary to correlate the interaction of flow and material in complex geometries to optimize modern blood pumps with respect to thrombogenicity. This does not only refer to the formation of fixed thrombi but also to emboli, thrombi that have detached from a surface, which travel through the bloodstream.

As human blood is a precious fluid, designers of blood pumps wish for reliable predictive thrombosis models to optimize the physiological compatibility of their devices. The use of computational fluid dynamics (CFD) techniques in blood pump design de-
creases the number of experiments that require the operation of prototypes with real human blood. A review on CFD analysis of blood pumps is given in [8].

The Taylor-Couette system is a well-investigated rotational device with respect to hemorheology and hemocompatibility [31]. Experimental and theoretical results for this device can be compared to computational ones to validate the predictive accuracy of a thrombosis model before it is applied to complex pump geometries.

1.2 Blood physiology

Human blood is a bodily fluid that is composed of blood cells suspended in an aqueous blood plasma which comprises about 55% of blood fluid’s volume. Around 99% of the blood cells consist of erythrocytes (red blood cells, RBCs) and the remaining blood cells are leukocytes (white blood cells) and thrombocytes (platelets). The biconcave disc-shaped RBCs play a significant role in oxygen transport and take up the main volume of the blood’s cellular contents. Leukocytes are spherical cells that are part of the immune system. Platelets, or thrombocytes are the smallest type of cells suspended in circulating blood. They are responsible for the initial formation of a plug to arrest bleeding and act as a catalyst in the blood coagulation process to fix the plug. In an inactivated state, platelets are smooth, biconvex disks, averaging 2 to 5 µm in diameter, 0.5 µm in thickness, and having a mean cell volume of 6 to 10 µm³ [36]. A healthy person has a concentration of between 140 and 400 · 10⁹ platelets per liter [49], occupying less than 0.3% of the blood’s volume. Platelets derive from bone marrow megakaryocytes and are relevant in primary hemostasis. A normal platelet’s life span is 7 to 11 days, during which it can be involved in hemostasis or a thrombotic event.

When blood vessels are damaged, the body’s hemostatic system creates a blood clot (thrombus) at the site of the injury to prevent bleeding. In certain situations, however, this system malfunctions and excessive clotting occurs. This malfunction, called thrombosis, is a serious medical complication because thrombi can break free, be transported downstream and occlude blood vessels. These thrombi can cause heart attacks or lead to stroke if they find their way into cerebral arteries.

The German pathologist Rudolf Virchow stated in 1862 that thrombus formation is primarily determined by three correlating parameters, known as Virchow’s triad. He recognized that the blood’s constitution, the properties of the surfaces in contact with blood, and abnormalities of blood flow are all important factors in the formation of thrombi [58]. Although almost 150 years have passed since then, Virchow’s triad is still widely accepted.

In order to maintain normal hemostatic activity, the pro- and anti-coagulant constituents in the blood need to be in an appropriate balance. Those are primarily platelets and coagulation factors, typically numbered by Roman numerals I-XIII. Thrombus for-
Blood physiology

1.2 Blood physiology

formation is achieved via platelet aggregation, deposition or due to either of two coagulation cascades. These three mechanisms, however, depend upon another.

1.2.1 Coagulation cascade

The coagulation cascade is triggered via one of two pathways: the contact activation pathway (intrinsic) and the tissue factor pathway (extrinsic, cf. figure 1.1). The final reaction in both coagulation cascades converts prothrombin (factor II) into thrombin (activated factor II, IIa), an enzyme which converts fibrinogen (I) into fibrin (Ia). For a more detailed explanation of the coagulation cascades, refer to Lind [32] or to Guyton and Hall [26].

![Coagulation cascade](image)

Figure 1.1: Coagulation cascade: Intrinsic and extrinsic pathways; HMWK: High-molecular-weight kininogen; PK: Prekallikrein; PL: Phospholipid

1.2.2 Hemocompatibility

Hemocompatibility characterizes the ability of a biomaterial in direct contact with blood to operate without inducing significant immune responses. Materials that are not hemocompatible are denoted by the term *thrombogenic*. 
In a human being, blood vessels are lined with endothelial cells which have antithrombogenic properties and prevent platelet adhesion. If the endothelium is injured subendothelial cells are exposed which initiates coagulation due to exposure of tissue factor (extrinsic pathway) and the presence of collagen, which supports the adhesion and activation of platelets.

When blood comes in contact with foreign material, proteins begin to adsorb to the foreign surface. Once adsorbed, the proteins start to interact with blood cells and platelets. Adsorption of high-molecular-weight kininogen (HMWK) can initiate the intrinsic coagulation cascade. Fibrinogen or von Willebrand factor (vWF) support platelet adhesion and aggregation. Thrombi formed at thrombogenic surfaces can detach and be transported downstream (emboli). Beside the formation of thrombi, thrombogenic materials can also destroy several components of circulating blood, activate immunologic reactions and denature plasma proteins. The ratio of blood volume to contact surface and the flow conditions play an important role in hemocompatibility [31].

1.2.3 Hemorheology

In order for platelets and coagulation factors to reach artificial surfaces or the site of an injury they must be transported there. In certain situations the composition of blood can influence the flow behavior of blood to a large extent. For a large class of fluids the local shear stress $\tau$ is proportional to the shear rate $\dot{\gamma}$

$$\tau = \mu \dot{\gamma}$$

(1.1)

where $\mu$ is the dynamic viscosity coefficient of the fluid. This linear relation was first derived by Isaac Newton, hence such fluids are called *Newtonian fluids*. In some situations, blood can be treated as a Newtonian fluid, and there are others where it cannot. Blood has interesting properties that are not only described by fluid mechanics but also by physiological phenomena that are mainly influenced by the presence of RBCs. Those effects are investigated in the multidisciplinary field of *hemorheology*.

The rheological properties of blood cells (e.g. deformability), are influenced by disease processes and extreme physiological conditions. Blood has a shear-thinning viscosity and also shows nonlinear viscoelastic behavior. The viscosity of blood varies with the temperature, disease state and the hematocrit Hct, which is also known as the erythrocyte volume fraction, and is defined as the proportion of blood volume that is occupied by red blood cells. Mottaghy et al. [37] verified that the apparent viscosity decreases with higher shear-rates. For shear rates higher than 200 $s^{-1}$ blood behaves approximately Newtonian (cp. fig. 1.2). In the case when all cellular contents are separated and only blood plasma is left ($Hct = 0\%$) the viscosity of blood is nearly independent of the shear rate [20]. As stated previously, blood in general belongs to the class of *non-Newtonian fluids*. 
1.2 Blood physiology

When blood is pumped through a tube of small diameter ($\varnothing < 0.3\text{mm}$) the apparent viscosity decreases, in what is known as the Fahraeus-Lindqvist or sigma effect. Another effect is the dependence of the hematocrit on the tube diameter, the so called Fahraeus effect. In addition, a cell-free layer near the wall as well as disproportionate distribution of cellular content and plasma at bifurcations can be observed. Those effects become stronger when the tube diameter becomes comparable to the diameter of a RBC [48].

The apparent (or effective) viscosity in a tube is defined as [44]

$$\mu_e = \frac{\pi D^4 \Delta p}{128 Q L},$$  \hspace{1cm} (1.2)

where $L$ is the length over which the pressure difference $\Delta p$ is measured, $Q$ is the flow rate and $D$ is the tube diameter. Note that for Newtonian fluids (1.2) simplifies to the Hagen-Poiseuille law by substituting $Q = \pi D^2 \bar{u}/4$, where $\bar{u}$ is the flow velocity averaged over the cross-section of the tube.

As stated above the rheological properties of blood are complex and not fully understood. Therefore for modeling purposes it is often assumed that the viscosity of blood can be approximated by the Cross equation [7]

$$\frac{\mu_0 - \mu}{\mu - \mu_\infty} = (K \dot{\gamma})^m,$$  \hspace{1cm} (1.3)
where $\mu_0$ refers to the asymptotic value of viscosity at very low shear rates and $\mu_\infty$ to that at very high shear rates. $K$ and $m$ are constant parameters. For $\mu \ll \mu_0$ and $\mu \gg \mu_\infty$ the Cross equation reduces to the power-law model

$$\mu = C \dot{\gamma}^{n-1},$$

by a rearrangement of parameters where $n$ is the so-called power-law index and $C$ is the consistency. Another model used in numerical studies of blood flow is the upper-convected Oldroyd model, also known as the Oldroyd-B model [9]. The Oldroyd-B model includes the Newtonian and Maxwell models, and covers the cases in which an elastic Maxwell type fluid is mixed with a Newtonian fluid. RBCs are considered to be an elastic polymer that is dissolved in a viscous solvent (plasma). The elastic properties are characterized by the dimensionless Weissenberg number

$$W_\text{s} = \lambda \dot{\gamma},$$

with $\lambda$ being the relaxation time of the RBCs. Detailed information on the Oldroyd-B model is given in [2.1.1] and the referenced literature.

### 1.2.4 Thrombus formation

The platelet plug is formed by three major platelet functions: adhesion, activation and aggregation.

**Activation**

Activation is triggered via shear stress or due to chemical stimulation with agonists such as collagen, adenosine diphosphate (ADP), thromboxane A$_2$ (TxA$_2$), thrombin and platelet-activating factor (PAF), which is a potent phospholipid activator. Platelets can also activate upon adhesion to a wall.

During activation, the platelets release coagulation factors and chemicals such as ADP. They undergo a morphological change from discs to a more spherical shape to support aggregation, and their surface membrane develops pseudopods with fibrin receptors to become more adherent to other activated platelets. In an activated state, platelets synthesize TxA$_2$ and other chemicals that, as well as the chemicals released during activation, can induce activation of other platelets nearby.

**Adhesion and Aggregation**

Platelet adhesion and aggregation are the essential mechanisms in the formation of thrombi. Adhesion refers to the coverage of surfaces with platelets and aggregation to the formation of cohesive platelet aggregates upon collision in the flow.
1.3 Prior work

Platelets adhere to proteins in non-endothelial surfaces via glycoproteins (GPs). Activated platelets can adhere to the surface already covered with activated platelets using fibrinogen as the connecting agent.

Aggregation of two or more platelets can occur in the flow field upon collision of activated platelets with other activated platelets or aggregates. Only activated platelets have fibrinogen receptors on their surfaces so platelets in a resting state cannot aggregate. More information on the mechanism of aggregation can be found in [21].

1.3 Prior work

Numerous research groups analyzed the phenomena of platelet transport, adhesion, activation and aggregation. Analytical solutions however could only be derived with simplifying assumptions such as constant diffusivities and reaction rates, steady-state behavior and simple flow conditions.

Affeld et. al. [3] reproduce the main characteristics of platelet deposition in a stagnation point flow experiment using a probabilistic cellular automata. The model considers only one agonist, thrombin, and the diffusivity coefficients are modeled as Brownian, hence depend only on temperature and particle size and material. Advective-diffusive transport of platelets and agonists is assumed to happen in a boundary layer at the wall which has a thickness of the average distance between platelets. The activation behavior of platelets is simulated in a shear flow, where the movement of the different kinds of particles is simulated using a random walk method (fig. 1.3). One agonist-emitting platelet is placed at the wall and a second platelet is floating by. The collisions of the platelet and the emitted agonist particles are counted in order to investigate the effect of wall distance and shear rate on the activation. The characteristic deposition pattern observed in experiments is well reproduced and the application of the method by projection of a cellular automata to critical wall regions of artificial organs is considered.

Sorensen et al. [53, 54] investigate the mechanisms leading to the formation and growth of mural thrombi on biomaterials. Their model consists of 7 coupled advection-diffusion-reaction equations and is developed for the simulation of two-dimensional platelet-biomaterial interactions. They attempt to simulate the following phenomena: platelet adhesion, agonist-induced platelet activation, platelet-platelet aggregation at surfaces, platelet-phospholipid-dependent thrombin generation and generation of platelet-released ADP and platelet-synthesized agonists (TxA₂). In Sorensen’s model, platelets have an inexhaustible capacity to generate TxA₂. Both, resting and activated platelets can adhere to exposed surfaces. Resting platelets can activate when adhering to the wall or due to an elevated agonist stimulation. Activated platelets can adhere to other activated platelets. It is observed that platelet activation and incipient aggregation occur within approximately 1–3s of platelet stimulation by a sufficiently high ADP concen-
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Therefore, Sorensen makes the assumption that activation takes place within 1 s of ADP stimulation above a certain threshold. The effects of growing thrombi on the flow field are neglected and the characteristic time for chemical reactions is considered much smaller than the characteristic time for fluid motion, thus a decoupled solution of the flow field and the transport and reaction of species is possible. Blood is assumed to be an incompressible Newtonian fluid that is homogenous rather than a colloidal suspension. The diffusivity of different substances is set to a constant value that is calculated based upon the mean shear stress of the steady flow field.

Lumped model parameters are fitted to a set of experimental data obtained for a parallel flow of whole blood over a collagen substrate. The "trained" model is then applied to additional test cases for which the predicted values agree very well with experiments.

1.4 Objectives and structure

The aim of this project is the development, implementation and evaluation of a mathematical model for the simulation of platelet adhesion, activation and aggregation. Appropriate numerical methods for the efficient solution of the partial differential equations arising from the model considerations will be presented and the computational results will be discussed and compared to data obtained from experiments.

In chapter 2, the modeling assumptions are discussed and subsequently the model equations are formulated. Chapter 3 introduces the time-discontinuous Galerkin formulation of the model equations that underlies the numerical solution with the stabilized space-time finite-element method. The linear system for the finite-element approximation is derived and implementation details are discussed. The qualitative comparison of
results obtained in numerical simulations with experimental data is reviewed in chapter 4, where the Taylor-Couette system is analyzed. An outlook is provided in chapter 5 in order to summarize further improvements to be made and to give an idea of possible applications of the model in the future. Because the numerical methods are discussed in general without referring to a specific finite-element code, a short manual of the XNS solver with listings is provided in appendix A.
Chapter 2

A continuum model for platelet adhesion, activation and aggregation

Thrombus formation is governed by flow, transport of species and reaction. As blood consists of a multitude of phases, and as the physiological processes that lead to thrombosis are not yet fully understood, it is currently impossible to obtain physically and physiologically exact models for computation. Several simplifications and assumptions have to be made to make the simulation on today’s high performance computers possible. In this chapter the governing equations for the simulation of blood flow are presented. It is shown that under certain assumptions blood can be treated as a single phase fluid. Subsequently, a model for platelet adhesion, activation and aggregation is presented.

2.1 Blood flow

2.1.1 Governing equations

Blood is treated as a viscous, incompressible fluid with a constant temperature that occupies a bounded domain $\Omega \subset \mathbb{R}^{n_{sd}}$, where $n_{sd}$ is the number of space dimensions. Pressure $p(x, t)$ and velocity $u(x, t)$ are governed by the incompressible Navier-Stokes equations:

\[
\rho \left( \frac{\partial u}{\partial t} + u \cdot \nabla u - f \right) - \nabla \cdot \sigma(u, t) = 0 \quad \text{on } \Omega, \\
\nabla \cdot u = 0 \quad \text{on } \Omega,
\]

(2.1)

where $f$ is the body force and $\rho$ is the constant density. For a Newtonian fluid the stress tensor $\sigma(u, p)$ reads as

\[
\sigma(u, p) = -pI + T, \\
T = 2 \mu \varepsilon(u), \\
\varepsilon(u) = \frac{1}{2} \left( \nabla u + (\nabla u)^T \right),
\]

(2.3)

(2.4)

(2.5)

where $\mu$ is the dynamic viscosity, $I$ is the unit tensor and $\varepsilon(u)$ is refered to as the rate of strain tensor.
2.1 Blood flow

In case of an Oldroyd-B model the Navier-Stokes equations are supplemented by a constitutive equation:

\[
\begin{align*}
\mathcal{T}_1 + \lambda \mathcal{T}_1 &= 2\mu_1 \varepsilon(u), \\
\mathcal{T}_2 &= 2\mu_2 \varepsilon(u), \\
\mathcal{T} &= \mathcal{T}_1 + \mathcal{T}_2, \\
\mu &= \mu_1 + \mu_2,
\end{align*}
\]

where \(\mu_1\) and \(\mu_2\) are the RBC and plasma viscosities, respectively and \(\mathcal{T}\) denotes an upper-convected derivative:

\[
\mathcal{T}' = \mathcal{T}' + u \cdot \nabla \mathcal{T}' - \left( \nabla u \mathcal{T} + \mathcal{T} \left( \nabla u \right)' \right). \tag{2.10}
\]

The Maxwell term in the constitutive equation is extremely difficult to handle numerically due to its advective character. The addition of the term for the Newtonian solvent diminishes the difficulties considerably but the problems arising in the discretization of advection-dominated problems still have to be expected [10].

2.1.2 Boundary conditions

The Dirichlet and Neumann-type boundary conditions are imposed on disjoint subsets of the boundary \(\partial \Omega = \partial \Omega^D \cup \partial \Omega^N:\)

\[
\begin{align*}
\mathbf{u} &= \mathbf{g}(x, t) & \text{on } \partial \Omega^D, \\
\hat{n} \cdot \mathbf{\sigma}(\mathbf{u}, p) &= \mathbf{h}(x, t) & \text{on } \partial \Omega^N,
\end{align*}
\]

where \(\hat{n}\) denotes the outward pointing normal to the boundary.

2.1.3 Modeling assumptions

It has to be shown that it is reasonable to neglect the dissolved particles’ inertia by assuming single-phase properties for blood. In fluid-particle flows, the Stokes number is defined as the ratio between the characteristic time of the flow field \(\tau = L/U\) and the momentum response time \(\tau_i\) of a particle:

\[
\text{St}_i = \frac{\tau_i}{\tau}. \tag{2.13}
\]

The particle Reynolds number \(\text{Re}_i\) is proportional to the particle radius, which means that \(\text{Re}_i \ll 1\) for blood cells (\(R_i < 20 \mu m\)).
Chapter 2 A continuum model for platelet adhesion, activation and aggregation

Under the assumption of spherical particles Stokes’ law holds for particle Reynolds numbers much smaller that unity. The particle response time is then given as

\[ \tau_i = \frac{2}{9} \frac{\rho_i R_i^2}{\mu}. \]  

(2.14)

It can be shown [14] that

\[ \frac{|u_i|}{|u|} \propto \frac{1}{1 + St_i} \]  \hspace{1cm} (2.15)

where \( u_i \) is the particle velocity and \( u \) is the carrier phase velocity. In the limit \( St_i \to 0 \) (velocity equilibrium) the particles have no influence on the flow and follow the streamlines whereas in the limit \( St_i \to \infty \) the particle movement is unaffected by the fluid. In case of blood flow, where the dissolved particles are small in radius, the particle response time is considerably small compared to the characteristic flow time, thus it is reasonable to neglect the influence of the particle inertia to the flow field. This makes a pre-computation of the flow field possible as the equations of thrombus formation and fluid flow show no coupling under the assumptions made.

2.2 Platelet adhesion, activation and aggregation

Thrombus formation is a complex process and is not yet fully understood. Assumptions have to be made to make a computational simulation possible. The present model considers blood that has citrate as an additive to inhibit the coagulation cascade. Hence there is only one strong platelet-released agonist, ADP, to be considered.

Platelets can be either in a resting state (RP) or in an activated state (AP), where both RP and AP can adhere to a surface. APs can also adhere to surfaces covered with already adhering APs or can irreversibly aggregate to form a doublet upon collision with another AP. Observations show that RPs activate instantly upon adhesion to the wall but can also activate in flow due to exposure to an agonist concentration above a threshold level for a certain time. It is further assumed that when a RP is activated, it releases all its agonist contents instantaneously.

Activation due to fluid shear stress is currently not included in the model to be presented, though it is an important activation factor in blood pump devices. One reason for this is that the computational effort for tracking exposure times in a continuum model is only possible at high computational cost. Another reason is the lack of a validated model relating shear-induced activation to the magnitude and duration of the applied shear stress.
2.2 Platelet adhesion, activation and aggregation

2.2.1 Governing equations

The generalized advection-diffusion-reaction (ADR) equation describes the transport of species $i$ in a bounded domain $\Omega \subset \mathbb{R}^{nd}$ due to advection, diffusion and reaction. It reads as

$$\frac{\partial c_i}{\partial t} + (\mathbf{u} \cdot \nabla) c_i = \nabla \cdot (D_i \nabla c_i) + S_i,$$

where $c_i = c_i(x, t)$ refers to the concentration of species $i$, $\mathbf{u}$ is the known velocity field of the surrounding fluid, $D_i = D_i(\dot{\gamma}, \text{Hct}, R_{RBC})$ is the (enhanced) diffusivity of species $i$ and $S_i$ represents a reaction term for species $i$, describing their creation and destruction.

Writing (2.16) for the concentrations of resting platelets [$RP$], activated platelets [$AP$] and one platelet-released agonist [$a_{pr}$] with the abbreviation $[i] := c_i$ leads to a system of partial differential equations, where the several equations are mutually coupled by the reaction terms $S_i$. 

---

Figure 2.1: Model: Platelet activation, adhesion and aggregation


2.2.2 Reaction terms

Activation of resting platelets

The reaction term $S_{RP}$ describes the transition of platelets from the resting to the activated state. It reads as

$$S_{RP} = -k_{pa} [RP],$$

(2.17)

where

$$k_{pa} = \begin{cases} 0 & \text{for } \Omega < 1 \\ \frac{\Omega}{t_{act}} & \text{for } \Omega \geq 1 \end{cases}$$

(2.18)

defines a threshold level for platelet activation [52]. The activation function is defined as

$$\Omega = \sum_j w_j \left[ \frac{a_j}{[a_{j\text{crit}}} \right],$$

(2.19)

where $t_{act}$ is a characteristic time for platelet activation and $[a_{j\text{crit}} = \text{const}$ is the critical concentration of agonist $j$. The agonist-specific weights $w_j$ are employed to model weak and strong agonists. As only one agonist $a_{pr}$ (ADP) is considered in the model, (2.18) and (2.19) reduce to

$$k_{pa} = \begin{cases} 0 & \text{for } [a_{pr}] < [a_{pr\text{crit}}} \\ \frac{[a_{pr}]}{[a_{pr\text{crit}} t_{act}} & \text{for } [a_{pr}] \geq [a_{pr\text{crit}},$$

(2.20)

where $[a_{pr\text{crit}} = \text{const}$ is the critical concentration of the platelet-released agonist.

The activation time is assumed as $t_{act} = 1 s$ according to Sorensen [52], who bases this choice on the observations of Frojmovic et. al. [19,18]. The form of the threshold function (2.20) shows that no activation takes place until the normalized agonist concentration reaches unity. Beyond this threshold for activation, the rate of platelet activation is allowed to increase linearly with agonist concentration.

Aggregation in flow

In-flow aggregation denotes the attachment of activated platelets to one another. In the model, the AP concentration increases due to the activation of RPs and decreases due to the formation of doublets from single platelets. Single platelets can also aggregate with doublets, triplets and bigger aggregates. However, Tandon and Diamond [55] showed that due to hydrodynamic forces the binding probability of single platelets to already formed aggregates is small, especially for quadruplets or aggregates of even more
platelets. In this model two aggregated APs fuse to form one AP, so we do not formally distinguish between APs and doublets.

To model the formation of doublets it is essential to model the capture frequency \( j_c \) of colliding platelets due to interparticle forces. Knowing the capture frequency the reaction term for the increase of AP due to activation and the decrease due to aggregation reads as

\[
S_{AP} = k_{pa} [RP] - \frac{1}{2} j_c [AP].
\]  
(2.21)

The capture efficiency \( \alpha_0 \in [0, 1] \) is an important parameter in platelet aggregation. It is defined as the ratio of the capture frequency to the collision frequency \( j_s \):

\[
\alpha_0 = \frac{j_c}{j_s}
\]  
(2.22)

This parameter is lumped and has to be determined from experimental measurements. In case of simple shear flow, Xia and Frojmovic [60] give a best fit for the capture efficiency in citrated platelet-rich plasma (PRP) as

\[
\alpha_0 = 53 G^{-1}
\]  
(2.23)

where \( G := \dot{\gamma} > 200 \text{ s}^{-1} \) is the average shear rate. Our model initially aims to simulate citrated whole blood including the influence of RBCs. It has been observed that their presence has an influence on the capture efficiency [22, 23]. However, as there is currently no suitable model for the capture efficiency in whole blood we will assume that \( \alpha_0 \propto G^{-1} \). A best fit for the proportionality constant has to be found by parameter estimation.

Smoluchowski [51] derived an expression for the two-body collision frequency between equal-sized spherical particles. Given an average platelet radius \( R_{pl} \) the collision frequency between APs reads as

\[
j_s([AP]) = \frac{32}{3} G R_{pl}^3 [AP].
\]  
(2.24)

It can be seen that under the assumption of Smoluchowski’s theory, the aggregation reaction term is proportional to the square of the AP concentration.

### Agonist generation

The reaction term \( S_{a_{pr}} \) describes the rate at which the agonist is generated from newly activated platelets:

\[
S_{a_{pr}} = \lambda_{a_{pr}} k_{pa} [RP].
\]  
(2.25)

The constant parameter \( \lambda_{a_{pr}} \) is the amount of \([a_{pr}]\) released per platelet. As it is assumed that each RP degranulates the same amount of agonist substance during activation this source term is proportional to \( S_{RP} \).
2.2.3 Boundary conditions

Based on the approaches of Grabowski et. al. [25] and Sorensen [52] the percentage of the free surface available for adhesion \( S(x, t) \) and the already covered surface \( M(x, t) \) are computed as

\[
M(x, t) = \int_0^t S(x, s) \left( k_{rs} [RP] + k_{as} [AP] \right) \, ds,
\]

\[ S(x, t) = 1 - \frac{M(x, t)}{M_\infty}, \tag{2.27} \]

where \( k_{rs} \) and \( k_{as} \) are lumped parameters that describe the adhesion behavior to surfaces of resting and activated platelets, respectively. They depend on the shear rate, the thrombogenic properties of the material and the platelet properties. \( M_\infty \) is the total capacity of the surface for platelets.

The wall thrombogenicity induces mass fluxes normal to foreign surface that are prescribed by Neumann type BCs:

\[
D_i \hat{n} \cdot \nabla c_i = J_i(x, t) \quad \text{for } x \in \text{'wall' } \subset \partial \Omega^W. \tag{2.28} \]

Adhesion of RPs to foreign surfaces is simulated by prescribing a reactive wall flux boundary condition:

\[
J_{RP}(x, t) = S(x, t) k_{rs} [RP]. \tag{2.29} \]

Note that this flux does not take adhesion to other platelets into account. Adhesion of APs to surfaces covered with already adhering APs and adhesion of APs to free surfaces is modeled as

\[
J_{AP}(x, t) = (S(x, t) k_{as} + (1 - S(x, t)) k_{aa}) [AP], \tag{2.30} \]

where \( k_{aa} \) describes the mutual aggregation of activated platelets at the wall and depends on the shear rate and platelet properties. Note that adhesion to deposited RPs is not considered in our model as it is assumed that RPs instantly activate and release their agonist content upon adhesion. Platelet-released agonist generation at the wall gives the last reactive wall flux BC:

\[
J_{a_{pr}}(x, t) = -\lambda_{a_{pr}} S(x, t) k_{rs} [RP]. \tag{2.31} \]

As in case of the reaction terms, this is proportional to the adhesive RP-flux at the boundary.
2.2 Platelet adhesion, activation and aggregation

2.2.4 Enhanced diffusivity

The effective diffusivity is modeled as

\[ D_i = D_{b,i} + D_s, \]  

(2.32)

where \( D_{b,i} \) is the Brownian diffusion coefficient of species \( i \) and \( D_s \) is an enhancement term that has to be modeled. For spherical particles, \( D_{b,i} \) is described by the Stokes-Einstein equation

\[ D_{b,i} = \frac{k_B T}{6 \pi \mu R_i}, \]  

(2.33)

where \( k_B \) refers to Boltzmann’s constant, \( T \) is the absolute temperature, \( \mu \) is the viscosity of the plasma and \( R_i \) is the particle radius.

Keller’s model \cite{30} takes the mass transfer induced by particle rotation into account. The diffusivity enhancement \( D_s \) is modeled as

\[ D_s = 0.18 \overline{R_{RBC}}^{-2} \dot{\gamma}, \]  

(2.34)

where \( \overline{R_{RBC}} = 2.75 \mu m \) is the averaged RBC radius \cite{53} and \( \dot{\gamma} \) is the shear rate. Unlike in other models based on rotational movement of RBCs (e.g. Antonini \cite{6}), (2.34) shows no dependency on the blood hematocrit \( \text{Hct} \). A generalized formulation for the application in an arbitrary-dimensional frame-invariant setting can be deduced as

\[ D_s = 0.18 \overline{R_{RBC}}^{-2} \sqrt{2 \text{tr} \varepsilon^2}. \]  

(2.35)

where \( \text{tr} \varepsilon^2 \) is the second invariant of the rate of strain tensor \cite{2.5}. Note that for fully developed channel flow, (2.34) and (2.35) are equivalent.

Zydney and Colton \cite{62} consider the hematocrit \( \text{Hct} \) but base their model on the influence of RBC deformation and collision:

\[ D_s = 0.15 R_{RBC,\text{max}}^2 \dot{\gamma} \cdot \text{Hct} (1 - \text{Hct})^{0.8}, \]  

(2.36)

where \( R_{RBC,\text{max}} = 4 \mu m \) is the maximum radius of a RBC.

2.2.5 Summary

The model for the simulation of platelet adhesion, activation and aggregation is based on three coupled advection-diffusion-reaction equations:

\[
\frac{\partial[R]}{\partial t} + (u \cdot \nabla) [R] = \nabla \cdot (D_R \nabla [R]) + (-k_{pa}) [RP],
\]

(2.37)

\[
\frac{\partial[AP]}{\partial t} + (u \cdot \nabla) [AP] = \nabla \cdot (D_{AP} \nabla [AP]) + k_{pa} [RP] - \frac{a_0}{2} j_s([AP]) \cdot [AP],
\]

(2.38)

\[
\frac{\partial[a_{pr}]}{\partial t} + (u \cdot \nabla) [a_{pr}] = \nabla \cdot (D_{a_{pr}} \nabla [a_{pr}]) + \lambda_{a_{pr}} k_{pa} [RP],
\]

(2.39)
and three reactive wall fluxes:

\[ J_{RP}(x, t) = S(x, t) k_{rs} [RP], \]
\[ J_{AP}(x, t) = (S(x, t) k_{as} + (1 - S(x, t)) k_{aa}) [AP], \]
\[ J_{apr}(x, t) = -\lambda_{apr} S(x, t) k_{rs} [RP]. \]

For the application of numerical methods, it is convenient to formulate the system of equations in a dimensionless manner. Non-dimensional variables are introduced as:

\[ t^* = t/t_{ref}, \quad x^* = x/l_{ref}, \quad [RP]^* = [RP]/[PLT]_\infty, \quad [AP]^* = [AP]/[PLT]_\infty \quad \text{and} \quad [a_{pr}]^* = [a_{pr}]/[a_{pr}]_{crit}, \]

where \( l_{ref} \) and \( t_{ref} \) are characteristic length and time scales respectively and \([PLT]_\infty\) denotes a reference value for the concentration of platelets (both, resting and activated) in blood. The dimensionless formulation of the system \( (2.37) - (2.39) \) reads as:

\[ \frac{\partial [RP]^*}{\partial t^*} + (u^* \cdot \nabla) [RP]^* = \nabla \cdot (D^*_{RP} \nabla [RP]^*) + (-k_{pa}^*) [RP]^*, \]
\[ \frac{\partial [AP]^*}{\partial t^*} + (u^* \cdot \nabla) [AP]^* = \nabla \cdot (D^*_{AP} \nabla [AP]^*) + k_{pa}^* [RP]^* - A_{gg} [AP]^2, \]
\[ \frac{\partial [a_{pr}]^*}{\partial t^*} + (u^* \cdot \nabla) [a_{pr}]^* = \nabla \cdot (D^*_{apr} \nabla [a_{pr}]^*) + A_{ct} k_{pa}^* [RP]^*, \]

where \( u^* = u/(l_{ref}/t_{ref}) \) and \( D^*_i = D_i/(l_{ref}^2/t_{ref}) \). It is assumed that \( j_s \) is proportional to \([AP]\). The activation reaction rate \( (2.18) \) takes the form

\[ k_{pa}^* = [a_{pr}]^* \cdot H([a_{pr}]^* - 1) \frac{t_{ref}}{t_{act}}, \]

where \( H \) refers to the Heaviside function, which is defined as:

\[ H(x) = \begin{cases} 
0 & \text{for } x \leq 0 \\
1 & \text{for } x > 0 .
\end{cases} \]

The dimensionless number

\[ \text{Act} := \frac{\lambda_{apr} [PLT]_\infty}{[a_{pr}]_{crit}} \]

can be seen as an indicator for platelet activation. The numerator is the amount of agonist substance in the system, including what is contained in the resting platelets. If \( \text{Act} \geq 1 \), activation due to an elevated agonist concentration is likely. If \( \text{Act} \ll 1 \), activation due to adhesion at the wall dominates and the influence of the activation in flow can be neglected. In this case the consideration of a platelet released agonist would be redundant.
The characteristic number $\text{Agg}$ indicates the likeliness of the formation of aggregates. It is defined as the upper limit of aggregates that can be formed in the characteristic time. This is the case when all platelets in the system are activated. It has the form:

$$\text{Agg} = \frac{t_{\text{ref}} \alpha_0}{2} j_i ([\text{PLT}]_\infty). \quad (2.49)$$

It can be seen that for low collision frequencies (resulting from lean platelet concentrations or low shear rates) and for a low capture efficiency aggregation becomes improbable. An interesting aspect here is the observation that for increasing shear rates the capture frequency goes up, the efficiency falls and vice versa for decreasing shear rates [60]. Under the assumption of Smoluchowski’ model for $j_i$ (2.24) and $\alpha_0 \propto G^{-1}$ the aggregation number $\text{Agg}$ becomes a lumped parameter for aggregation in flow that is constant in space and time.

The dimensionless formulation of the boundary conditions (2.29)–(2.31) requires some small modifications in the formulation for the surface coverage (2.26) and the free surface percentage (2.27).

$$M^*(x, t) = \frac{[\text{PLT}]_\infty}{M_\infty} \int_0^t S(x, t) (k_{rs} [\text{RP}]^* + k_{as} [\text{AP}]^*) \, dt, \quad (2.50)$$

$$S(x, t) = 1 - M^*(x, t). \quad (2.51)$$

Surface reaction rates are made dimensionless as $k_i^* = k_i (l_{\text{ref}} / t_{\text{ref}})$ where $i \in \{rs, as, aa\}$. The reactive wall fluxes can now be written as:

$$J_{\text{RP}}^*(x, t) = S(x, t) k_{rs}^* [\text{RP}]^*, \quad (2.52)$$

$$J_{\text{AP}}^*(x, t) = (S(x, t) k_{as}^* + (1 - S(x, t)) k_{aa}^*) [\text{AP}]^* \quad (2.53)$$

$$J_{\text{AP}}^*(x, t) = -\text{Act} S(x, t) k_{rs}^* [\text{RP}]^*. \quad (2.54)$$
Chapter 3

Numerical methods

The system of partial differential equations (PDEs) defining the model is solved using the finite-element method (FEM). The discretization and solution is done in several steps (cf. figure 3.1).

The first step is preprocessing, where a mesh for the simulation is generated and initial conditions are specified. This is followed by a time step loop, which contains a nested nonlinear iteration loop where a linear system of equations is formed and solved. The formation of this system is done on element-level and the contributions of each element are assembled to form the global system. After reaching convergence for a predefined number of time-steps, data is written out and can be used for postprocessing procedures like visualization.

<table>
<thead>
<tr>
<th>preprocessing</th>
<th>mesh generation</th>
<th>initial conditions</th>
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</thead>
<tbody>
<tr>
<td>time-step loop</td>
<td>nonlinear iteration loop</td>
<td>formation of the linear system of equations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>formation of element-level matrices and residuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>assembly of element-level contributions into node level quantities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>solution of linear system of equations</td>
</tr>
<tr>
<td>postprocessing</td>
<td>data output</td>
<td>visualization</td>
</tr>
</tbody>
</table>

Figure 3.1: Major components of a FEM simulation code

The body of the solution procedure presented is in its main components common for all kinds of equations. What is unique for each PDE system to be solved is the formation of element-level matrices and residuals that are assembled to form the linear system of equations that rises from the discretized model equations. The concepts involved herein are presented in this chapter. A comprehensible introduction to the FEM is given in [17]. More advanced topics are covered in [28] and [16]. For details on the implementation of a FEM code refer to [50].
3.1 The stabilized space-time finite-element method

The space-time method extends the concepts of finite elements to the time domain instead of utilising semi-discrete finite-difference schemes. For advection-dominated problems, Galerkin formulations may result in spurious oscillations causing a loss of accuracy and stability. This happens especially in the presence of discontinuities. Stabilization can be achieved by perturbation of the weighting functions in upwind-direction to produce accurate and oscillation-free solutions. However, these formulations do not prevent overshooting and undershooting along discontinuities.

In this section a Galerkin formulation of the advection-diffusion-reaction equations will be derived. This formulation will be then extended to a Petrov-Galerkin type with a perturbation that stabilizes the formulation. Another perturbation term is added to the formulation for discontinuity capturing.

3.1.1 Problem statement

The scalar advection-diffusion-reaction equation and its initial and boundary conditions read as

\[ u_t + (a \cdot \nabla) u - \nabla \cdot (\kappa \nabla u) = f \quad \text{on} \quad \Omega \subset \mathbb{R}^n, \]
\[ u = g \quad \text{on} \quad \partial \Omega^D, \]
\[ \hat{n} \cdot \kappa \nabla u = h \quad \text{on} \quad \partial \Omega^N, \]
\[ u = u_0 \quad \text{on} \quad \Omega \text{ at } t_0, \]

(3.1) (3.2) (3.3) (3.4)

where \( u \) is the quantity to be transported (concentration, temperature, ...) , \( a \) is the advective velocity and \( \kappa \) is the diffusivity.

3.1.2 Time-discontinuous Galerkin formulation

The time-discontinuous Galerkin method allows the interpolation fields to be discontinuous at discrete points in time, which allows to solve the system by advancing step-by-step in time instead of solving for all time intervals at once.

The time domain is partitioned in \( n_{st} \) sub-intervals \( I_n = (t^n, t^{n+1}) \), \( n = 0, 1, \ldots, n_{st} - 1 \) and space-time slabs are defined as

\[ Q_n = \Omega \times I_n, \quad n = 0, 1, \ldots, n_{st} - 1. \]

(3.5)

where each space-time slab has a smooth boundary \( P_n := \partial \Omega \times I_n \). Let \( T^h(\Omega) \) be a regular partition of \( \Omega \) into \( n_e \) convex element subdomains \( \Omega^e \neq \emptyset \) such that

\[ \overline{\Omega} = \bigcup_{e=1}^{n_e} \overline{\Omega^e} \quad \text{and} \quad \Omega^e \cap \Omega^f = \emptyset \quad \text{for} \ e \neq f. \]

(3.6)
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Space-time element domains can then be defined as

$$Q_n^e = \Omega^e \times I_n, \quad \Omega^e \in T^h(\Omega), \quad n = 0, 1, \ldots, n_{st} - 1$$

with a smooth boundary $P_n^e := \partial \Omega^e \times I_n$.

Piecewise continuous approximations in space and discontinuous approximations in time are considered. The finite-element spaces for the trial and weighting functions are defined as follows:

$$S^h = \bigcup_{n=0}^{n_{st}} S_n^h, \quad S_n^h = \left\{ u^h | u^h \in H^1(Q_n^e) \, , \, u^h|_{Q_n^e} \in P_k(Q_n^e) \, , \, u^h|_{P_n^D} = g \right\}$$

$$V^h = \bigcup_{n=0}^{n_{st}} V_n^h, \quad V_n^h = \left\{ w^h | w^h \in H^1(Q_n^e) \, , \, w^h|_{Q_n^e} \in P_k(Q_n^e) \, , \, w^h|_{P_n^D} = 0 \right\}$$

where $P_k$ denotes the space of polynomials of total degree $\leq k$ and $P_n^D = \partial \Omega^D \times I$ is the Dirichlet part of the space-time boundary. Note that continuity over $Q_n^e$ implies continuity only in space. For continuity in time a jump condition has to be introduced. For the formulation of this jump condition it is useful to utilize the notation

$$u^h_\pm := \lim_{\epsilon \to 0} u^h(t^n \pm \epsilon), \quad w^h_+ := \lim_{\epsilon \to 0} w^h(t^n + \epsilon).$$

The Galerkin form with jump condition is then given as: for $n = 0, 1, \ldots, n_{st} - 1$ find $u^h \in S^h$ such that: $\forall w^h \in V^h$,

$$\int_{Q_n^e} w^h \left( u^h + a \cdot \nabla u^h - \nabla \cdot (\kappa \nabla u^h) - f \right) \, dQ + \int_{\Omega} w^h_+(u^h_+ - u^h_-) \, d\Omega = 0.$$ (3.11)

with the initial condition $u^h(x, t^0) = u_0(x, t)$. The continuity in time which is weakly enforced by the last integral allows the propagation in time from one slab to another.
3.1 The stabilized space-time finite-element method

Solution values at the end of the previous time interval can be interpreted as initial conditions for the solution of the subsequent time interval. Integrating (3.11) by parts and substitution of (3.3) yields

\[
\int_{Q_n} w^h\left(u_t^h + a \cdot \nabla u^h - f\right) dQ + \int_{Q_n} \nabla w^h \cdot (\kappa \nabla u^h) dQ \\
+ \int_{\Omega} w_n^e(u_n^e - u_n^e) d\Omega = \int_{P_n^e} w^h h dP.
\]

(3.12)

where \(P_n^e = \partial \Omega^N \times I\) is the Neumann part of the space-time boundary. The superscript is dropped such that \(u^h\) and \(w^h\) are referred to as \(u\) and \(w\) hereafter.

Centered discretization of the advection term leads to oscillations in advection-dominated problems. In stabilized formulations the weighting functions are perturbed such that more weight is shifted in upwind direction.

![Galerkin vs. Petrov-Galerkin weighting functions](image)

Figure 3.3: Galerkin vs. Petrov-Galerkin weighting functions

The following notation for the differential operator and the residual operator is employed for the compact formulation of residual-based numerically stable schemes:

\[
\mathcal{L}(u) = u_t + a \nabla u - \nabla \cdot (\kappa \nabla u)
\]

(3.13)

\[
\mathcal{R}(u) = \mathcal{L}(u) - f.
\]

(3.14)

Adding residual-based stabilization terms to (3.12) yields:

\[
\int_{Q_n} w\left(u_t + a \cdot \nabla u - f\right) dQ + \int_{Q_n} \nabla w \cdot (\kappa \nabla u) dQ \\
+ \sum_e \int_{Q_n} \mathcal{P}(w) \tau_{stab}^e \mathcal{R}(u) dQ \\
+ \int_{\Omega} w_n^e(u_n - u_n^e) d\Omega = \int_{P_n^e} w h dP.
\]

(3.15)

where \(\tau_{stab}^e\) is a stabilizing parameter which depends on the spatial discretization and \(\mathcal{P}(w)\) is a differential operator that depends on the stabilization scheme used (see table 3.1).
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<th>Stabilization</th>
<th>$\mathcal{P}(w)$</th>
</tr>
</thead>
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<td>Streamline-Upwind Petrov-Galerkin (SUPG)</td>
<td>$a \cdot \nabla w$</td>
</tr>
<tr>
<td>Galerkin/Least-squares (GLS)</td>
<td>$L(w)$</td>
</tr>
<tr>
<td>Adjoint GLS (AGLS)</td>
<td>$-L^*(w)$</td>
</tr>
</tbody>
</table>

Table 3.1: Overview: Stabilization schemes

Brooks and Hughes [12] have shown that for rectangular elements the perturbation of the weighting functions does not affect the weighting of the diffusion term and expect the contribution for well-shaped elements to be negligible. It can be shown that upwind-type discretizations induce numerical diffusion and vice versa [16]. Because for a fine enough mesh no stabilization is necessary it is obvious that the stabilizing parameter $\tau_{\text{stab}}$ must vanish when the mesh is more and more refined. The choice of this parameter is discussed in Donea and Huerta [16] and the literature referenced therein. Shakib [47] proposed a locally second-order accurate formula

$$\tau_{\text{stab}}^e = \frac{h_e}{2\|a\|^2} \left( 1 + \frac{1}{\text{Pe}^2} \right)^{-1/2},$$

(3.16)

where $h_e$ is the mesh size and $\text{Pe} = \|a\| \frac{h_e}{2\kappa}$ is the mesh Peclet number. He also proposed a slightly modified version for fourth-order accuracy. Unfortunately this fourth-order accuracy does not apply to higher dimensions or general advection-diffusion systems.

To preclude overshooting and undershooting around sharp internal and boundary layers, a second perturbation term in direction of the solution gradient is added to the weighting function. The stabilized formulation with discontinuity capturing reads as

$$\int_{Q_n} \int_{Q_n} w \left( \mathbf{u}_n + a \cdot \nabla \mathbf{u} - f \right) dQ + \int_{Q_n} \nabla w \cdot (\kappa \nabla \mathbf{u}) dQ + \sum_e \int_{Q_n^e} \mathcal{P}(w) \tau_{\text{stab}}^e \mathcal{R}(u) dQ + \sum_e \int_{Q_n^e} \tau_{\text{DC}}^e \left( \frac{\nabla u}{\|\nabla u\|^2} \cdot \nabla w \right) dQ$$

$$+ \int_\Omega w \left( a_n^e - u_n^e \right) d\Omega = \int_{P_n^e} w h dP,$$

(3.17)

where $\tau_{\text{DC}}^e$ depends on the discontinuity capturing scheme to be used. Tezduyar and Park [57] present several different choices for $\tau_{\text{DC}}^e$. For example the EC1 scheme arises from the choice

$$\tau_{\text{DC}}^e = h_g \text{ sgn} (\|a_g\|^2) \left( \frac{\|a\|^2}{\|a_g\|^2} - 1 \right),$$

(3.18)
3.1 The stabilized space-time finite-element method

where \( h_e \) is the element length in the direction of the solution gradient and \( \mathbf{a}_g \) is the velocity component parallel to the solution gradient.

To account for a general, non-linear case, \( u_{n+1} \) is computed using increments.

\[
\begin{align*}
    u_{0}^{n+1} &= u_{n}, \\
    u_{i+1}^{n+1} &= u_{i}^{n+1} + \Delta u_{i+1}^{n+1}.
\end{align*}
\]  

(3.19) (3.20)

The increment based time-discontinuous formulation is:

\[
\begin{align*}
    & \int_{Q_n} w \left( \Delta u_{i+1,}^{n+1} + \mathbf{a} \cdot \nabla \Delta u_{i+1}^{n+1} \right) dQ \\
    & \quad + \int_{Q_n} \nabla w \cdot \left( \kappa \nabla \Delta u_{i+1}^{n+1} \right) dQ + \int_{\Omega} w_{\mathbf{n}}^{n} \Delta u_{i+1}^{n} d\Omega \\
    & \quad + \sum_{e} \int_{Q_e} P(w) \tau_{stab}^{e} L(\Delta u_{i+1}^{n+1}) dQ + \sum_{e} \int_{Q_e} \tau_{DC}^{e} \frac{\nabla \Delta u_{i+1}^{n+1}}{\|g\|_2} \cdot \nabla w dQ \\
    & \quad = \int_{Q_n} w f dQ + \int_{Q_n} w h dP - \int_{Q_n} w \left( u_{i,i}^{n+1} - \mathbf{a} \cdot \nabla u_{i}^{n+1} \right) dQ \\
    & \quad - \int_{Q_n} \nabla w \cdot (\kappa \nabla u_{i}^{n+1}) dQ - \int_{\Omega} w_{\mathbf{n}}^{n} (u_{n}^{n} - u_{n}^{n}) d\Omega \\
    & \quad - \sum_{e} \int_{Q_e} P(w) \tau_{stab}^{e} R(u_{i}^{n+1}) dQ - \sum_{e} \int_{Q_e} \tau_{DC}^{e} \frac{\nabla u_{i}^{n+1}}{\|g\|_2} \cdot \nabla w dQ. \tag{3.21}
\end{align*}
\]

where \( g := \nabla u_{i}^{n+1} \) is the linearized solution gradient.

3.1.3 Finite-element approximation

A finite element approximation over a space-time slab is chosen that is piecewise polynomial in space and time. For \((x, t) \in Q_n,\)

\[
\Delta u^h(x, t) = \sum_{j=1}^{N_n} N_j(x) \left( \Theta_1(t) \Delta \tilde{u}_j^t + \Theta_2(t) \Delta u_{j+1}^t \right). \tag{3.22}
\]

\( N_j(x) \) is the spatial shape function at node \( j. \) The nodal values of \( \Delta u^h \) for node \( j \) at \( t^r \) and \( t^{r+1} \) are \( \Delta \tilde{u}_j^t \) and \( \Delta u_{j+1}^t \) respectively. \( \Theta_1(t) \) and \( \Theta_2(t) \) are the time interpolation functions defined for the linear case as

\[
\Theta_1(t) = \frac{1}{\Delta t} (t^{r+1} - t), \quad \Theta_2(t) = \frac{1}{\Delta t} (t - t^r). \tag{3.23} \tag{3.24}
\]
Chapter 3 Numerical methods

The test functions $w^h$ are defined similarly as $N_j(x) \Theta_1(t)$ and $N_j(x) \Theta_2(t)$, $i = 1, \ldots, n_n$. Substitution of the approximation and test functions in (3.21) and sorting for knowns and unknowns gives rise to an equation system $K \mathbf{u} = \mathbf{p}$, where $K$ is the stiffness matrix, $\mathbf{u}$ is the vector of unknowns and $\mathbf{p}$ is the right hand side (residual) vector. Dirichlet boundary conditions are imposed by constraining the appropriate degree-of-freedom in the linear equation system.

3.1.4 Computation of element matrices

In practical implementations of the finite-element method, integration is done at the element level. The contributions of each element are later topologically assembled to form the stiffness matrix $K$ and the residual $p$. This assembly process requires knowledge of the connectivity in the underlying finite element mesh and is represented by an assembly operator $A^e$:

\[ K = A^e K^e, \]

\[ p = A^e p^e, \]

where the element level matrix and residual are defined as

\[
K_{AB}^e = \int_{Q_e^*} N_A (N_B + a \cdot \nabla N_B) \, dQ + \int_{Q_e^*} \kappa \nabla N_A \cdot \nabla N_B \, dQ \\
+ \int_{Q_e^*} \mathcal{P}(N_A) \tau_{stab}^e L(N_B) \, dQ + \int_{Q_e^*} \tau_{DC}^e \frac{\nabla N_B}{||g||} \cdot \nabla N_A \, dQ \\
+ \int_{\Omega^e} (N_A \cdot N_B) (t^n_e) \, d\Omega, \quad A, B = 1, \ldots, n_{en}
\]

(3.27)

\[
p^e_A = \int_{Q_e^*} N_A f \, dQ + \int_{\mathcal{P}_e^* \cap \mathcal{P}_h^e} N_A h \, dP \\
- \sum_{B=1}^{n_{en}} \left( K_{AB}^e (u^n_{A,B}) - \int_{\Omega^n} (N_A \cdot N_B) (t^n_e) u^n_{A,B} \, d\Omega \right), \quad A = 1, \ldots, n_{en}
\]

(3.28)

The shape functions $N_i(\xi, \vartheta)$, $i = 1, \ldots, n_{en}$ for each element $Q_e^*$ are defined on a reference element $Q^*$ in terms of normalized coordinates $(\xi, \vartheta)$, where $n_{en}$ is the number of space-time nodes per element. A triangular ($n_{en} = 6$) space-time reference element with shape functions is shown in figure 3.4.
3.1 The stabilized space-time finite-element method

\[ N_1(\xi, \eta, \vartheta) = \xi (1 - \vartheta)/2 \]
\[ N_2(\xi, \eta, \vartheta) = \eta (1 - \vartheta)/2 \]
\[ N_3(\xi, \eta, \vartheta) = (1 - \xi - \eta)(1 - \vartheta)/2 \]
\[ N_4(\xi, \eta, \vartheta) = \xi (1 + \vartheta)/2 \]
\[ N_5(\xi, \eta, \vartheta) = \eta (1 + \vartheta)/2 \]
\[ N_6(\xi, \eta, \vartheta) = (1 - \xi - \eta)(1 + \vartheta)/2 \]

Figure 3.4: Triangular space-time reference element and shape functions

The integration on element-level is done by mapping from physical coordinates \((x, t)\) to reference coordinates \((\xi, \vartheta)\). The coordinate transformation is given as

\[ (x, \vartheta) = \sum_{i=1}^{n_{en}} N_i(\xi, \vartheta)(x^i, t^i) \]  \(3.29\)

The Jacobian matrix of an element is needed to transform derivatives from the physical to the reference coordinates. It is defined as

\[ J_e = \frac{\partial(x, t)}{\partial(\xi, \vartheta)}. \]  \(3.30\)

Using the inverse of \(J_e\), the conversion of the derivatives reads as

\[ \frac{\partial}{\partial(\xi, \vartheta)} = J_e^{-1} \frac{\partial}{\partial(x, t)}. \]  \(3.31\)

The determinant of the element Jacobian is required to transform the integral:

\[ \int_{\Omega_e} \cdots dx \, dt = \int_{\Omega_e} \cdots |J_e| \, d\xi \, d\vartheta. \]  \(3.32\)

Integration over the reference domain is approximated by quadrature via

\[ \int_{\Omega} \psi(\xi, \vartheta) \, d\xi \, d\vartheta \approx \sum_{i=1}^{n_{quad}} \psi(\xi^i, \vartheta^i) \, w^i, \]  \(3.33\)

where \(n_{quad}\) is the number of quadrature points and \(\xi^i\) and \(w^i\) are the quadrature points and weights respectively. Optimal choices for \((\xi^i, w^i), \, i = 1, \ldots, n_{quad}\) are known as Gaussian quadrature rules. For a comprehensive compilation of quadrature rules for different element types refer to [61].
3.2 Extension to advection-diffusion-reaction systems

For the solution of a coupled set of advection-diffusion-reaction equations the stiffness matrix has to be extended to solve for \( n_{\text{DOF}} \) degrees of freedom (DOF) \( u^{(k)} \), \( k = 1, \ldots, n_{\text{DOF}} \) simultaneously. For coupled equations we have \( A \in \mathbb{R}^{N \times N} \) where \( N = n_n \cdot n_{\text{DOF}} \). Given the mapping

\[
\mathcal{I} : \mathbb{N}^3 \mapsto \mathbb{N}^2 : \mathcal{I}(A, B, k) = ((A - 1) n_{\text{DOF}} + k, (B - 1) n_{\text{DOF}} + k),
\]  

(3.34)

the contributions to the stiffness matrix are computed as

\[
K_{(A,B,k)}^e = \int_{Q_e} N_A (N_{B,t} + a \cdot \nabla N_B) dQ + \int_{Q_e} \kappa^{(k)} \nabla N_A \cdot \nabla N_B dQ
\]
\[
+ \int_{Q_e} \mathcal{P}(N_A) \tau_{\text{stab}}^{(k),e} \mathcal{L}(N_B) dQ + \int_{Q_e} \tau_{\text{DC}}^{(k),e} \frac{\nabla N_B}{\|g^{(k)}\|_2} \cdot \nabla N_A dQ
\]
\[
+ \int_{Q_e} (N_A \cdot N_B)(r_i^n) d\Omega, \quad A, B = 1, \ldots, n_n, \ k = 1, \ldots, n_{\text{DOF}}.
\]  

(3.35)

where \( \kappa^{(k)} \) and \( g^{(k)} \) are the diffusivity coefficient and the solution gradient for the \( k \)-th DOF, respectively. The contributions to the residual are computed in a similar manner:

\[
P_{(A-1)n_{\text{DOF}}+k} = \int_{Q_e} N_A f^{(k)} dQ + \int_{P_e \cap P_n} N_A h^{(k)} dP
\]
\[
- \sum_{B=1}^{n_n} \left( K_{AB}^{e} (u_i^{(k),n+1})_B - \int_{Q_e} (N_A \cdot N_B)(r_i^n) u_A^{(k),n+1} d\Omega \right), \quad A = 1, \ldots, n_n, \ k = 1, \ldots, n_{\text{DOF}}.
\]  

(3.36)

Note that for each DOF a reaction term \( f^{(k)} \) and a Neumann flux \( h^{(k)} \) is specified. It is also necessary to compute the stabilization parameters for each DOF. The assembled system \( \mathbf{K} \mathbf{u} = \mathbf{p} \) is solved for the vector of unknowns \( \mathbf{u} \in \mathbb{R}^{n_{\text{DOF}} n_n} \) of the form \( \mathbf{u} = (u_1^{(1)}, \ldots, u_1^{(n_{\text{DOF}})}, \ldots, u_n^{(1)}, \ldots, u_n^{(n_{\text{DOF}})}) \).

3.3 Reactive wall boundary condition

The boundary conditions presented in section 2.2.3 require the numerical approximation of an integral of the form:

\[
M(x, t) = \int_0^t S(x, t) f(u^{(i)}(x, t)) \, dt,
\]  

(3.37)

\[
S(x, t) = 1 - M(x, t).
\]  

(3.38)
3.3 Reactive wall boundary condition

Reactive wall fluxes in the model contribute to the right hand side of the linear system. The fluxes depend on the free surface percentage which has to be updated after each time-step. Lourens [33] uses a rectangular approximation to update the integral as:

\[ M_n = M_{n-1} + S_{n-1} f(u_{n-1}) \Delta t, \]  \hspace{1cm} (3.39)

where \( n \) is the number of the current time-step. This kind of update is very inaccurate because the function \( f \) is approximated by a constant function which has the value of the previous timestep. We implemented a trapezoidal rule which provides more accuracy. The integral update is computed as

\[ M_n = M_{n-1} + \frac{S_{n-1} f(u_{n-1}^{(i)}) + S_n f(u_n^{(i)})}{2} \Delta t, \]  \hspace{1cm} (3.40)

where \( M_n \) and \( S_n \) are defined as \( M(x, t^n) \) and \( S(x, t^n) \) respectively. More details about the integration methods and error estimates can be found in Press et al. [45]. Using (3.38) the variable \( M \) can be eliminated. The update simplifies to:

\[ S_n = 1 - M_n = S_{n-1} - \frac{S_{n-1} f(u_{n-1}^{(i)}) + S_n f(u_n^{(i)})}{2} \Delta t. \]  \hspace{1cm} (3.41)
Chapter 4

Application to Taylor-Couette systems

The Taylor-Couette system is one of the most-studied examples of fluid flow exhibiting the spontaneous formation of dynamical structures. It is an interesting device for the study of platelet adhesion, activation and aggregation, since it can generate multiple flow situations at once that are critical in practical applications like centrifugal blood pumps (e.g. recirculation areas, stagnation point flow).

There has been a large number of experimental and theoretical studies of flow between concentric cylinders. The earliest studies were conducted in the late 19th century by Mallock [34, 35] and Couette [13]. In the early 20th century, Taylor [56] made a huge effort in the development of hydrodynamic instability theory by investigating the stability of Couette flow.

For low angular velocities, the flow is in a steady and purely azimuthal laminar state, which is known as circular Couette flow. Taylor [56] showed that when the angular velocity of the inner cylinder is increased above a certain threshold, the circular Couette flow becomes unstable and a secondary steady state known as the Taylor vortex flow develops, which is characterized by axisymmetric toroidal vortices. Further increase of the rotational speed leads to more complex states, such as the wavy vortex flow. If the two cylinders counterrotate, then spiral Vortex flow can arise. Beyond a certain angular velocity the flow becomes turbulent.

Analytical solutions of the Navier-Stokes equations for the Taylor-Couette system can only be derived under certain simplifying assumptions. If the derivation of an analytical solution is impossible or too challenging it might more convenient to solve the Navier-Stokes equations numerically. A computational analysis of the Taylor vortex flow is presented in section 4.2.

4.1 Geometry

The annulus configuration in figure 4.1 shows a classical Taylor-Couette system where the radius of the interior cylinder is given as $R_1$ and the gap width between the two concentric cylinders is given as $L = R_2 - R_1$. The ratio of the two radii is defined as $\phi = R_1/R_2$. The cylindrical gap is supposed to be infinitely extended, thus the Taylor problem is independent of the axial direction $z$. 
4.1 Geometry

![Geometry of a Taylor-Couette system](image)

Figure 4.1: Geometry of a Taylor-Couette system

4.1.1 Circular Couette flow

For theoretical analysis it is convenient to formulate the governing equations in cylindrical coordinates \((r, \theta, z)\). Neglecting external forces, the Navier-Stokes equations for incompressible flow of a Newtonian fluid read as:

\[
\rho \left( \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} \right) + \nabla p - \mu \nabla^2 \mathbf{u} = 0,
\]

\[
\nabla \cdot \mathbf{u} = 0, \tag{4.1}
\]

with the dynamic viscosity \(\mu\) and the pressure \(p\). The vector \(\mathbf{u} = (u_r, u_\theta, u_z)\) holds the velocities in radial, azimuthal and axial direction.

Boundary conditions are given by the no-slip conditions at the inner and outer cylinder walls:

\[
\mathbf{u}(r = R_1) = (0, \Omega_1 R_1, 0), \tag{4.3}
\]

\[
\mathbf{u}(r = R_2) = (0, \Omega_2 R_2, 0). \tag{4.4}
\]

The circular Couette flow in the cylindrical gap describes the laminar steady state \((u_0, p_0)\) of a viscous fluid between two infinitely long concentric cylinders. Assuming that
Chapter 4 Application to Taylor-Couette systems

\[ u_{0} = u_{z0} = 0, \quad u_{\theta 0} = u_{00}(r) \] and \[ p_{0} = p_{0}(r) \], the Navier-Stokes equations (4.1) simplify to

\[ 0 = \frac{\partial p_{0}}{\partial r} - \rho \frac{u_{n0}}{r^{2}}, \] (4.5)

\[ 0 = \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u_{n0}}{\partial r} \right) - \frac{u_{n0}}{r^{2}} = \frac{\partial}{\partial r} \left( \frac{1}{r} \frac{\partial}{\partial r} (ru_{\theta 0}) \right), \] (4.6)

\[ 0 = \frac{1}{r} \frac{\partial u_{\theta 0}}{\partial \theta}. \] (4.7)

The azimuthal component (4.6) is then integrated twice with respect to \( r \) to find a general solution for the Couette velocity profile:

\[ u_{\theta 0}(r) = C_{1} r + C_{2} \frac{1}{r}. \] (4.8)

Matching the integration constants \( C_{1} \) and \( C_{2} \) to the boundary conditions (4.3) and (4.4) yields

\[ C_{1} = \frac{\Omega_{2} - \Omega_{1} \phi^{2}}{1 - \phi^{2}}, \]

\[ C_{2} = \frac{R_{2}^{2} (\Omega_{1} - \Omega_{2})}{1 - \phi^{2}}. \]

To derive an average shear rate, the angular velocity is introduced as \( \omega = u_{\theta 0}/r \), which satisfies \( \omega(R_{1}) = \Omega_{1} \) and \( \omega(R_{2}) = \Omega_{2} \). The average shear rate is then defined as:

\[ G = \frac{1}{L} \int_{R_{1}}^{R_{2}} \frac{d\omega}{dr} dr = \frac{2(\phi^{2} \Omega_{1} + \Omega_{2})}{1 - \phi^{2}}. \] (4.9)

Körfer [31] however uses a different definition in her experiments that was derived by Mottaghy [38]:

\[ G_{Mottaghy} = \frac{2(R_{2}^{2} \Omega_{1} + R_{1}^{2} \Omega_{2})}{R_{2}^{2} - R_{1}^{2}} = \frac{2(\phi^{2} \Omega_{1} + \Omega_{2})}{1 - \phi^{2}}. \] (4.10)

4.1.2 Instabilities

The flow is characterized by the ratio of radii and the Reynolds numbers of the cylinders:

\[ \text{Re}_{i} = \frac{\Omega_{i} R_{i} L}{v}, \quad i = 1, 2, \] (4.11)
4.1 Geometry

Figure 4.2: Regime diagram: Redrawn from [5]. Dashed lines indicate transition boundaries that are difficult to establish from visual observation alone since there is no abrupt change in the appearance. Dotted lines indicate the expected, but not yet observed, continuation of several boundaries.

where $\nu$ is the kinematic viscosity and $\Omega_i$ are the rotational speeds of the corresponding cylinders.

Andereck et. al. [5] analyzed the different flow states for a broad range of Reynolds numbers. A regime diagram of the different flow types emerging in Taylor-Couette systems is shown in figure 4.2.

A single dimensionless number that characterizes the flow in a Taylor-Couette system is the Taylor number $Ta$. As there is no unique definition for this characteristic number we will use the definition used in Körfer [31]:

$$Ta = \frac{\phi \Omega_1}{\nu} \left( \frac{R_1^2 + R_2^2}{2} \right)^{1/2}.$$ (4.12)

The square of the Taylor number $Ta^2$ indicates the ratio of the centrifugal force to the viscous force. At a critical value of $Ta^2_{cr} = 1,708$ (that is $Ta = 41.3$), it is observed that the circular Couette flow changes into the Taylor vortex flow with steady and rotationally symmetric ($\partial/\partial \theta = 0$) perturbations, so called Taylor vortices. A perturbation
Chapter 4 Application to Taylor-Couette systems

\[
\mathbf{u}, p = (u_0, p_0) + \epsilon \cdot (u', p')
\]  \hspace{1cm} \text{(4.13)}

can be used to derive the perturbation differential equations \[40\]. Substituting (4.13) in (4.1) and (4.2) and linearizing the resulting system by neglecting powers of \(\epsilon\) results in

\[
-\rho \frac{2u_0}{r} u'_0 = \frac{\partial p'}{\partial r} + \mu \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u'_0}{\partial r} \right) + \frac{\partial^2 u'_0}{\partial z^2} - \frac{u'_0}{r^2} \right),
\]  \hspace{1cm} \text{(4.14)}

\[
\rho \left( \frac{\partial u_0}{\partial r} + \frac{u_0}{r} \right) u'_r = \mu \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u'_0}{\partial r} \right) + \frac{\partial^2 u'_0}{\partial z^2} - \frac{u'_0}{r^2} \right),
\]  \hspace{1cm} \text{(4.15)}

\[
0 = -\frac{\partial p'}{\partial z} + \mu \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u'_z}{\partial r} \right) + \frac{\partial^2 u'_z}{\partial z^2} \right),
\]  \hspace{1cm} \text{(4.16)}

\[
0 = \frac{\partial u'_r}{\partial r} + \frac{u'_r}{r} + \frac{\partial u'_z}{\partial z}.
\]  \hspace{1cm} \text{(4.17)}

Because the perturbed solution also satisfies the no-slip conditions, the perturbations vanish at the cylinder walls. Thus the boundary conditions are given as:

\[
u'(r = R_1) = 0, \]
\[
u'(r = R_2) = 0.
\]  \hspace{1cm} \text{(4.18, 4.19)}

The pressure is independent of the problem and can be determined up to a constant \[41\]. By solving the system (4.14)–(4.17) it is possible to construct solutions for Taylor vortex flows. A comprehensive derivation can be found in \[56\].

4.2 Simulation of blood flow in Taylor-Couette systems

In \[1.2.3\] it was shown that blood behaves approximately Newtonian for high shear rates. We try to reproduce experimental results conducted at an average shear rate of \(G = 600 \text{ s}^{-1}\), thus the assumption of a Newtonian viscosity model for the simulation of the blood flow holds.

4.2.1 Flow parameters

The Taylor-Couette system has an inner cylinder radius of 17.85 mm and an outer cylinder radius of 19.45 mm. Material properties for blood are taken from measurements. The viscosity and density of blood are chosen as \(3.5 \cdot 10^{-6} \text{ kg mm}^{-1} \text{ s}^{-1}\) (see fig. \[1.2\]) and \(1.055 \cdot 10^{-6} \text{ kg mm}^{-2}\) respectively.

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4.2 Simulation of blood flow in Taylor-Couette systems

Parameter & Value & Unit \\
--- & --- & --- \\
Inner radius $R_1$ & 17.85 mm & \\
Outer radius $R_2$ & 19.45 mm & \\
Ratio $\phi$ & 0.91774 & - \\
Gap width $L$ & 1.6 mm & \\
Blood viscosity $\mu_{\text{blood}}$ & $3.5 \cdot 10^{-6}$ kg mm$^{-1}$ s$^{-1}$ & \\
Blood density $\rho_{\text{blood}}$ & $1.055 \cdot 10^{-6}$ kg mm$^{-3}$ & \\

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing entities (PEs)</td>
<td>$n_{pe}$</td>
<td>1,024 -</td>
</tr>
<tr>
<td>SUPG-Stabilization</td>
<td>$\tau_{\text{stab}}$</td>
<td>$\tau_{\text{Shakib}} \cdot 1.0$ -</td>
</tr>
<tr>
<td>GMRES iterations</td>
<td>$n_{\text{inner}}$</td>
<td>70 -</td>
</tr>
<tr>
<td>GMRES restarts</td>
<td>$n_{\text{outer}}$</td>
<td>2 -</td>
</tr>
<tr>
<td>nonlinear iterations</td>
<td>$n_{\text{it}}$</td>
<td>4 -</td>
</tr>
<tr>
<td>time-step size</td>
<td>$\Delta t$</td>
<td>$5 \cdot 10^{-3}$ s</td>
</tr>
</tbody>
</table>

Table 4.1: Summary: Taylor-Couette flow parameters

4.2.2 Simulation setup and realization

The flow simulation is performed on JUGENE, a supercomputer based on the Blue Gene/P system built by IBM for the Jülich Research Centre in Germany. It reaches a peak processing power of 222.8 TFLOPS (Rpeak) with 65,536 PowerPC 450 cores, clocked at 850 MHz. The Navier-Stokes equations are solved in parallel using XNS, the in-house finite-element flow solver at the Chair for Computational Analysis of Technical Systems (CATS) at RWTH Aachen University. Parameters for the solver are chosen as shown in table 4.2.

Computational mesh

The mesh shown in figure 4.3 is a hexahedral mesh with equal directional spacing. A discretization of 25 nodes in radial, 50 in axial and 200 in circumferential direction results in a structured mesh with 234,024 hexahedral elements and 248,750 nodes or 497,500 space-time nodes. The mesh is partitioned into 1,024 subdomains to allow parallel computing.
Section 4.2.3 Boundary conditions

Symmetry (slip) boundary conditions ($\hat{n} \cdot \nabla u = 0$) are prescribed on the top and bottom part of the boundary. For the cylinder walls a no-slip condition is imposed by velocity constraints: $u(r = R_1, t) = \Omega_1 R_1$ and $u(r = R_2, t) = 0$.

Figure 4.4: Taylor-Couette system: Boundaries and associated normal vectors

Section 4.2.4 Results

In the CFD analysis the Taylor vortex flow was reproduced for flows above $Ta = 41.3$. Below the critical Taylor number no vortex formation could be observed which perfectly
4.3 Simulation of platelet adhesion, activation and aggregation

agrees with experimental observations for the Taylor-Couette system. A cross-sectional plot showing the Taylor vortices in the gap can be seen in figure 4.5. When the rotational velocity in the simulation is slowly ramped down from supercritical to subcritical Taylor numbers the Taylor vortices slowly disperse and the flow state merges into circular Couette flow.

Körfer conjectured that the regions of highest shear stress can be found near the cylinder walls and in the center of the Taylor vortices. She expects high platelet concentrations in that area because erythrocytes tend to migrate to regions of low shear stress. Our simulations however show that Körfer’s statement regarding the shear stresses is not entirely correct, because it is entirely based on the velocity gradient in the (r,z)-plane. The magnitude of the velocity gradients there coincide with the regions identified by Körfer, but when the whole 3D velocity field is considered they do not (fig. 4.6). Further experimental investigation is therefore required to identify the RBC distribution in Taylor-vortex flow.

4.3 Simulation of platelet adhesion, activation and aggregation

For the simulation of platelet adhesion, activation and aggregation in Taylor-Couette systems, the model equations (2.43)–(2.45) are solved using a pre-computed advective velocity field. In the simple case of circular Couette flow, the analytical solution (4.8) can be evaluated for each grid point to obtain the velocity, but when it comes to Taylor vortex flow the Navier-Stokes equations are solved as shown in section 4.2.
The concentration of platelets in blood is in the range $1.4 - 4.0 \cdot 10^5 \, pl/mm^3$ (cf. section 1.2). For the simulations, an initial homogenous platelet concentration of $[PLT]_\infty = 3.0 \cdot 10^5 \, pl/mm^3$ is assumed, where 5% of the platelets are in a pre-activated state and 95% remain resting. It is assumed that due to human platelet heterogeneity and deterioration only a certain percentage of the platelets can activate. Körfer observed in her experiments that around 50% of the platelets are inert which leads to 47.5% of resting platelets to be modeled in our simulations. The initial agonist concentration is set to zero. Under these assumptions made for the blood’s constitution dimensionless concentrations of $[RP]_0 = 0.475$, $[AP]_0 = 0.05$ and $[a_{pr}]_0 = 0.0$ are initially set.

It is further assumed that the shear-dependent effect of the RBCs on the transport applies only to the larger platelets and not to the small agonist particles. Therefore the diffusivity of the platelets is enhanced using Keller’s model (2.34) with an average shear rate of $G = 600 \, s^{-1}$, which gives an enhancement of $D_s = 8.1675 \cdot 10^{-4} \, mm^2 \, s^{-1}$. Because
4.4 Parameter estimation

this enhancement is several orders of magnitude higher than the platelets’ Brownian diffusivity, the latter is neglected. The diffusivity of the agonist substance (ADP) is assumed to be Brownian in accordance to Sorensen et. al. [53], Table 4.3 gives an overview of the different diffusion coefficients.

<table>
<thead>
<tr>
<th>Component</th>
<th>Diffusivity $[\text{mm}^2 \text{s}^{-1}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet</td>
<td>$D_{RP}, D_{AP}$</td>
</tr>
<tr>
<td>Agonist (ADP)</td>
<td>$D_{a pr}$</td>
</tr>
</tbody>
</table>

Table 4.3: Overview: Diffusivities of different species

As the lumped parameters Agg, Act, $M_{\infty}$, $k_{rs}$, $k_{as}$ and $k_{aa}$ are unknown, they have to be estimated directly from measurements or indirectly by fitting simulation results to experimental studies.

4.4 Parameter estimation

4.4.1 The surface capacity $M_{\infty}$

Brash et. al. [11] estimate the maximum capacity under the assumption of spherical resting platelets in densest packing without taking spreading and formation of pseudopodia during activation into account. They estimate the capacity as $M_{\infty} = 25 \cdot 10^4 \text{pl/mm}^2$.

SEM measurements show that the diameter of adherent activated platelets varies between 3 and 4 $\mu$m. This diameter coincides with values taken from literature such as Gawaz [21]. For an estimation of the surface capacity for adhesion an average diameter of 3.5 $\mu$m is assumed. Without taking a possible densest packing of spherical objects into account (cf. fig. 4.7) this leads to a maximum capacity of around $M_{\infty} = 8 \cdot 10^4 \text{pl/mm}^2$, which is considerably lower that Brash’s estimation.

4.4.2 The platelet activation parameter Act

In accordance with Sorensen et. al. [53], we use the estimation of Adams and Feuerstein [2] for the amount of agonist (ADP) released per platelet. Based on their measurements we assume that each resting platelet is capable of releasing $\lambda_{a pr} = 2.4 \cdot 10^{-8} \text{nmol/pl}$ upon activation. The critical ADP level $[a_{pr}]_{crit} = 2 \cdot 10^{-3} \text{nmol/mm}^3$ is also taken from Sorensen. Computing the platelet activation parameter as in equation (2.48) for a reference platelet concentration of $[PLT]_{\infty} = 3.0 \cdot 10^5 \text{pl/mm}^3$ gives

$$\text{Act} = \frac{\lambda_{a pr} [PLT]_{\infty}}{[a_{pr}]_{crit}} = 3.6,$$
Chapter 4 Application to Taylor-Couette systems

which is greater than unity and thus activation of resting platelets has to be considered in the model.

4.4.3 Fitting the remaining parameters

The adhesion rates $k_{rs}$, $k_{as}$ and $k_{aa}$ as well as the aggregation parameter $\text{Agg}$ cannot be measured directly. Experiments conducted by Körfer [31] show that after one minute of laminar shear with $G = 600 \, s^{-1}$ the platelet count drops to an average of 92% of its initial value. This percentage decreases to 60% after 10 minutes of shear before it reaches a minimum of 47% after around 15 minutes. Continuation of this experiment does not lead to a significant decrease of the platelet count. SEM measurements show that after 10 minutes of laminar shear with $G = 600 \, s^{-1}$, about 56.85% of the surface is covered with adherent platelets.

As shown in section 4.1.1 the laminar Couette flow is a purely azimuthal and axisymmetric flow state, thus the flow velocity does not influence the transport in radial direction. In this case the Couette flow experiments simplifies to a one-dimensional diffusion problem. In order to fit the model parameters to the experimental data a diffusion problem is solved in 2D on a rectangular mesh (fig. 4.8) that has the same wall distance $L = 1.6 \, mm$ as the gap in the Taylor-Couette system to be investigated.

For laminar flow we expect a uniform surface coverage $S(t)$ at the wall without the formation of coverage patterns. Sorensen et. al. [54] found adhesion rates for flow over collagen which is a very aggressive material for platelet adhesion. As the material investigated by Körfer (polystyren, PS) is much less aggressive, the values for collagen ($k_{rs} = 3.7 \cdot 10^{-2} \, mm \, s^{-1}$, $k_{as} = k_{aa} = 4.6 \cdot 10^{-2} \, mm \, s^{-1}$) give an upper bound for parameter estimation. The lower bound is a perfectly hemocompatible material (e.g. endothelial
cells) that does not support adhesion \((k_{rs}, k_{as} \to 0)\). The surface adhesion rates \(k_{rs}\) and \(k_{as}\) have a strong influence on the surface coverage. High adhesion rates result in a surface coverage that approaches its maximum (full coverage) in relatively short periods of time whereas the surface covers much slower with platelets if low adhesion rates are chosen. Figure 4.9 shows the influence of adhesion rates on the free surface percentage in absence of activation and aggregation effects.

The effects of platelet adhesion, activation and aggregation are described by a system of partial differential equations that depend on the 6 parameters Act, Agg, \(M_\infty\), \(k_{rs}\), \(k_{as}\) and \(k_{aa}\) that are considered constant in space and time. We estimated Act and \(M_\infty\) from measurements. The other parameters cannot be measured directly, so we have to estimate those parameters from given measurements. Measurements are provided for \(S(t)\), \(P(t)\) and \(A(t)\) (tab. 4.4) where \(S(t)\) is the free surface percentage averaged over the boundary, \(P(t)\) and \(A(t)\) are the domain averaged total (non-adherent) platelet concentration and the aggregate concentration respectively.

The vector of unknown parameters \(x = (Agg, k_{rs}, k_{as}, k_{aa})\) is subject to fitting. As for the lack of a complete set of measurements for the free surface percentage it is defined that missing measurements perfectly agree with simulation results: \(S_{i, \text{meas}} = S_{i, \text{sim}}\) for \(i \neq 4\) (cp. tab. 4.4). A functional is defined as

\[
F_i(x) = \|((S, P, A)_{\text{meas}} - (S, P, A)_{\text{sim}})\|^2, \quad i = 1, \ldots, 6. \tag{4.20}
\]

The nonlinear least squares problem can then be formulated as: Find \(x^* \in \mathbb{R}^4\) such that

\[
\|F(x^*)\|_2 = \min_{x \in \mathbb{R}^4} \|F(x)\|_2, \tag{4.21}
\]

where \(x^*\) is the optimal choice for the parameter vector \(x\). Expansion in Taylor series around a point \(x^d\) leads to

\[
F(x) = F(x^d) + F'(x^d)(x - x^d) + O(\|x - x^d\|^2). \tag{4.22}
\]
If terms of higher order are neglected, substitution of (4.22) in (4.21) yields a linear least squares problem
\[ \| F'(x^k)s^k + F(x^k) \|_2 = \min_{s \in \mathbb{R}^4} \| F'(x^k)s + F(x^k) \|_2, \] (4.23)
where \( s^k = x - x^k \) is the residual vector. Solving the linear least squares problem gives an equation for \( s^k \):
\[ F'(x^k)^T F'(x^k) s^k = -F'(x^k)^T F(x^k). \] (4.24)
Given an initial guess \( x^0 \) the iteration
\[ s^k = -\left( F'(x^k)^T F'(x^k) \right)^{-1} F'(x^k)^T F(x^k), \] (4.25)
\[ x^{k+1} = x^k + s^k \] (4.26)
defines the Gauss-Newton method. For a detailed analysis of this method please refer to Dahmen and Reusken [15] or to Nocedal and Wright [39].

Application of this method to a parameter fitting problem requires extraction of the results from a simulation record. As this is very time-consuming, a good initial guess is needed to reduce the number of iterations. A trial and error approach was used to guess the initial parameter vector as \( x^0 = 10^{-3} \cdot (2.0, 1.5, 1.6, 2.0)^T \). The solution plot for this set of parameters is already close to experimental data as can be seen in figure 4.10.

The Jacobian in (4.23) is computed by finite differences, which requires five simulations per iteration, one for the actual solution at \( x^k \), and four more for the computation of the Jacobian \( F'(x^k) \). The simulations are done in parallel using XNS with 2 PEs per job on a 22 node Apple Xserve G5 cluster with 44 CPUs and 46 GB RAM in total. The post-processing does not require lots of computational power and is done on a conventional workstation using Paraview for the extraction and visualization of simulation results and a MATLAB-implementation of the algorithm presented above for the computation of the next approximation.

Note: The method described above provides a powerful tool that helps improving a good initial guess. It is however not guaranteed that these parameters will actually make sense in a physiological context. As we can see in table 4.5, the first two parameter sets qualitatively agree with experimental observations. In the subsequent iterations parameters are found that provide an even better fit to the measurements but make no physiological sense (\( k_{rs} > k_{as}, k_{aa} < 0 \)). In order to obtain optimal parameters it might be necessary to weight or even exclude measured data points in the optimization, or to manually correct the parameter quality between two subsequent iterations.

In the following simulations, the parameters obtained for \( i=1 \) are considered as qualitatively good enough parameters for first simulations. A plot of the solution for these parameters in comparison with the initial guess and measurements is shown in figure 4.11.
4.5 Results for circular Couette flow

It is observed that in the first 40 seconds of the simulation for circular Couette flow at \( G = 600 \text{ s}^{-1} \), reaction takes place in the vicinity of the reactive cylinder walls only. If the agonist concentration exceeds the threshold level for activation, an explosive increase of AP sets in because RP that activate release additional agonist substance to the flow field (4.12). This leads to a chain reaction that activates all RPs that are not considered inert, thus \([RP]^*\) drops to zero. The increased AP concentration supports aggregate formation and further adhesion to the walls.

4.6 Results for Taylor vortex flow

It can be seen that in case of Taylor vortex flow, the distribution of adhering platelets is not uniform as in case of the circular Couette flow. Comparing the SEM images for laminar flow with Taylor vortex flow (fig. 4.13, 4.14) reveals a specific adhesion pattern at the cylinder walls. We could not reproduce this pattern formation in our simulations because we have a continuum model which may not include all physiological phenomena leading to the adhesion patterns. Anyway, our computations were performed on a mesh that is coarse compared to the scales where the pattern formation is observed. We can identify a global distribution of adhering platelets but not specific patterns on a microscopic scale.

As we use the velocity field with the pre-computed Taylor vortex flow as input for our simulations, we simulate the platelet adhesion, activation and aggregation processes on the same mesh (fig. 4.3). The computations are again done on JUGENE with 2,048 processors which is twice the number of processors we used in the simulation of the Taylor vortex flow.

Figure 4.15 shows a \((r,z)\)-plane cut of the resting platelet concentration after 10 seconds of Taylor vortex flow at \( Ta = 43.5 \). It can be seen that many resting platelets are trapped in the recirculation areas in the center of the vortices and can only get to the walls by advective transport. The stagnation point region where all platelets are

| \( i \) | \( \text{Agg} \) | \( k_{\text{rs}}^* \) | \( k_{\text{as}}^* \) | \( k_{\text{aa}}^* \) | \( ||s'||_2 \) |
|-----|-------|-------|-------|-------|-------|
| 0   | \( 2.0 \cdot 10^{-3} \) | \( 1.5 \cdot 10^{-3} \) | \( 1.6 \cdot 10^{-3} \) | \( 2.0 \cdot 10^{-3} \) | \( 1.5 \cdot 10^{-3} \) |
| 1   | \( 1.8 \cdot 10^{-3} \) | \( 2.0 \cdot 10^{-3} \) | \( 2.1 \cdot 10^{-3} \) | \( 3.4 \cdot 10^{-3} \) | \( 2.3 \cdot 10^{-3} \) |
| 2   | \( 1.8 \cdot 10^{-3} \) | \( 3.4 \cdot 10^{-3} \) | \( 2.6 \cdot 10^{-3} \) | \( 5.1 \cdot 10^{-3} \) | \( 4.2 \cdot 10^{-2} \) |
| 3   | \( 2.2 \cdot 10^{-3} \) | \( 3.51 \cdot 10^{-2} \) | \( 2.3 \cdot 10^{-3} \) | \( -2.57 \cdot 10^{-2} \) | \(-\) |

Table 4.5: Iteration history for "optimal" parameters
transported straight to the wall by advection shows a conspicuous decrease of resting platelets due to adhesion.

SEM imaging shows that in circular Couette flow, an average of $45.5 \cdot 10^3$ platelets adhere per square-millimeter whereas in Taylor vortex flow only around $30.5 \cdot 10^3$ adherent platelets are found, which is about one third less (fig. 4.16). Our simulations however could not reproduce these results. This may be due to effects that are currently not considered in the model. Further improvements, simulations and evaluations will have to be made to see if the model can qualitatively reproduce these measured values.
4.6 Results for Taylor vortex flow

Figure 4.9: Influence of adhesion rates on the free surface percentage in absence of activation and aggregation effects:
(1) $k_{rs}^* = 3.7 \cdot 10^{-2}, k_{as}^* = 4.6 \cdot 10^{-2}$ (collagen)
(2) $k_{rs}^* = 3.7 \cdot 10^{-3}, k_{as}^* = 4.6 \cdot 10^{-3}$
(3) $k_{rs}^* = 3.7 \cdot 10^{-4}, k_{as}^* = 4.6 \cdot 10^{-4}$
(4) $k_{rs}^* = 3.7 \cdot 10^{-5}, k_{as}^* = 4.6 \cdot 10^{-5}$
(5) $k_{rs}^* = k_{as}^* = 0.0$ (perfectly hemocompatible)
Figure 4.10: Measured quantities and solution with initially guessed parameters. Solid lines indicate simulation results. Diamonds indicate measured averages and intervals for 5 experiments each.
Figure 4.11: Measured quantities and solution with optimized parameters. Dashed lines and diamonds indicate the solution for initially guessed parameters and measurements as in fig. 4.10, respectively. Solid lines indicate simulation results for the optimized parameters.
Figure 4.12: Explosive change of averaged concentrations in circular Couette flow.
Figure 4.13: Adherent platelets in Couette flow. Different zoom factors after 10 min with $\dot{\gamma} = 600 \text{ s}^{-1}$.
Figure 4.14: Adherent platelets in Taylor vortex flow. Different zoom factors after 10 min with $\dot{\gamma} = 600 \text{s}^{-1}$
4.6 Results for Taylor vortex flow

Figure 4.15: RP concentration in Taylor vortex flow (Ta = 43.5) after 10 seconds.

Figure 4.15: RP concentration in Taylor vortex flow (Ta = 43.5) after 10 seconds.
Figure 4.16: Number of platelets remaining in blood (N=20) and number of wall adherent platelets (N=5) after 10 min of Taylor vortex and simple laminar flow at shear rate of $\dot{\gamma} = 600 \text{ s}^{-1}$. Data according to Körfer [31].
Chapter 5

Outlook

The model presented and analyzed in this thesis represents the basic mechanisms of platelet activation, adhesion and aggregation but does not consider certain aspects. It needs to be extended to improve its predictiveness before it can someday be applied to improve the design of artificial organs such as rotational blood pumps with respect to thrombosis. The effects to be included are:

- the effect of RBC migration on platelet transport
- shear-induced platelet activation
- modeling of thrombus formation and embolization
- coagulation cascade, platelet-synthesized agonist TxA2 (cf. Sorensen [52])

The purpose of this chapter is to collect ideas for future improvements of the model and to present and discuss other researchers’ approaches.

5.1 The effect of RBC migration on platelet transport

It is known that RBC migration has a strong effect on platelet transport. Aarts et al. [1] investigated that in flowing blood platelets are concentrated near the wall and red blood cells in the center. This effect is called platelet skimming and is observed in presence of erythrocytes. Körfer [31] concludes that erythrocytes reside in areas of low shear and high velocities, whereas the rigid platelets are pushed into regions of high shear. Transferred to the Taylor-Couette system this means that the platelet concentration in the vicinity of walls and in the center of the vortices should be perceptibly higher than in other flow regions. This however has to be proved by measurements. It is possible to include this effect into our model by initially specifying a realistic non-homogenous platelet concentration profile and by hindering diffusion of platelets into low shear regions using enhanced diffusivities (see section 2.2.4) that are not computed with a mean shear rate but with a spatially and temporally varying shear rate.
5.2 Shear-induced platelet activation

Holme et al. [27] found out that the effect of shear-induced platelet activation is significant for high shear rates. In a general purpose model the shear-induced platelet activation requires treatment, as this event is relevant to cardiovascular devices such as rotary blood pumps. Alemu and Bernstein [4] base their model for activation on the theory of platelet damage, incorporating cumulative effects of stress history and past damage (senescence). They applied their model to a three dimensional model of a mechanical heart valve to predict platelet damage from total stress and quantify the thrombogenic potential of cardiovascular devices.

5.3 Modeling of thrombus formation and embolization

The model as presented does not consider thrombus growth, detachment and the associated alterations of the flow field. Future work involves the evaluation and realization of a reasonable strategy to track the formation of thrombi and to predict emboli.

Pivkin et al. [43] use a particle model rather than a continuum model and continuously update the geometry of the thrombus with regard to size and shape. Goodman et al. [24] predict the progression of thrombus growth and thromboembolization in low-shear devices such as hemodialyzers, oxygenators etc. using a continuum model similar to that of Sorensen et al. [53]. The model requires the computation of the flow field for each time-step to account for the alterations caused by thrombi. At each time step, if the volume of adherent platelets within a grid cell is greater than the grid cell volume, the grid cell is designated as thrombus and the viscosity within that grid cell is increased by a factor of $10^5$. The grid cells neighboring the thrombus grid cell adopt the surface flux boundary condition.
Statutory declaration

I hereby declare that this thesis has been written by myself and that any parts of this thesis which are quoted from or based on other sources have been acknowledged as such without exception.

This thesis has been neither presented to any institution for evaluation nor previously published in its entirety or in parts.

Hiermit versichere ich, die vorliegende Arbeit selbständig und unter ausschließlicher Verwendung der angegebenen Literatur und Hilfsmittel erstellt zu haben.

Die Arbeit wurde bisher in gleicher oder ähnlicher Form keiner anderen Prüfungsbehörde vorgelegt und auch nicht veröffentlicht.

Aachen, November 26, 2008

Christian Waluga
Bibliography


Abbreviations

TxA$_2$  thromboxane A$_2$
ADP  adenosine diphosphate
ADR  advection-diffusion-reaction
AGLS  adjoint Galerkin/Least-squares
AP  activated platelet
BTT  bridge to transplantation
CFD  computational fluid dynamics
DOF  degree of freedom
FEM  finite-element method
GLS  Galerkin/Least-squares
GP  glycoprotein
HMWK  high-molecular-weight kininogen
PAF  platelet-activating factor
PDE  partial differential equation
PE  processing entity
PRP  platelet-rich plasma
RBC  red blood cell
RNG  reference node group
RP  resting platelet
SUPG  streamline-upwind Petrov-Galerkin
VAD  ventricular assist device
vWf  von Willebrand factor
Symbols

\((\cdot)^*\) dimensionless variable
\((\cdot)_{ref}\) reference value
\([i]\) abbreviation for concentration of component \(i\): \([i] := c_i\)
\([a_j]_{\text{crit}}\) critical concentration of agonist \(j\)
\([PLT]_{\infty}\) reference value for the concentration of platelets in blood
\(\alpha_0\) capture efficiency
\(L(u)\) differential operator
\(\mathcal{P}_k\) space of polynomials of total degree \(\leq k\)
\(\mathcal{R}(u)\) residual operator
\(S_h\) finite-element trial function space
\(T^h(\Omega)\) regular partition of \(\Omega\)
\(\mathcal{V}^h\) finite-element weighting function space
\(\Delta p\) pressure difference
\(\dot{\gamma}\) shear rate
\(\kappa\) diffusivity
\(\lambda\) relaxation time
\(\lambda_{\text{apr}}\) amount of agonist substance released per platelet
\(J_e\) element jacobian
\(K\) stiffness matrix
\(K^e\) element matrix
\(\mu\) dynamic viscosity
\(\nu\) kinematic viscosity
\(\Omega\) activation function
\(\Omega\) bounded spatial domain
\(\Omega_1\) rotational speed (inner cylinder)
\(\Omega_1\) rotational speed (outer cylinder)
\(\bar{u}\) averaged velocity
\(\partial\Omega^D\) Dirichlet part of the boundary
\(\partial\Omega^N\) Neumann part of the boundary
\(\phi\) ratio of radii
\(\rho\) density
\(\nabla\) upper convected derivative
\(\tau\) characteristic time
\(\tau\) shear stress
\(\tau^D_{\text{DC}}\) discontinuity capturing parameter
\(\tau^\text{stab}\) stabilizing parameter
\(\tau_i\) momentum response time of a particle
\(I\) unit tensor
## Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mathbf{T}$</td>
<td>shear stress tensor</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>stress tensor</td>
</tr>
<tr>
<td>$\mathbf{e}$</td>
<td>rate of strain tensor</td>
</tr>
<tr>
<td>$\text{Re}_i$</td>
<td>Reynolds number of a particle</td>
</tr>
<tr>
<td>$\text{St}_i$</td>
<td>Stokes number of a particle</td>
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<tr>
<td>$T_{\text{crit}}$</td>
<td>critical Taylor number</td>
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<tr>
<td>$\Theta_i$</td>
<td>time interpolation function</td>
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<tr>
<td>$\mathbf{n}$</td>
<td>outward pointing normal vector</td>
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<tr>
<td>$\varnothing$</td>
<td>tube diameter</td>
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<tr>
<td>$\hat{\mathbf{n}}$</td>
<td>normalized time</td>
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<tr>
<td>$\mathbf{g}$</td>
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<td>$f$</td>
<td>body force</td>
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<td>$g$</td>
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<td>diameter</td>
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<td>diffusivity of component $i$</td>
</tr>
<tr>
<td>$D_s$</td>
<td>diffusivity enhancement</td>
</tr>
<tr>
<td>$D_{b,i}$</td>
<td>Brownian diffusion coefficient of species $i$</td>
</tr>
<tr>
<td>$G$</td>
<td>average shear rate: $G := \frac{\mathbf{v}}{\mathbf{v}}$</td>
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<td>$g$</td>
<td>Dirichlet boundary function</td>
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<tr>
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<td>Heaviside (unit step) function</td>
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<td>adhesion rate of APs to a foreign surface</td>
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<td>characteristic length</td>
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<td>$L$</td>
<td>gap width</td>
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<tr>
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<td>surface capacity for platelets</td>
</tr>
<tr>
<td>$n_e$</td>
<td>number of elements</td>
</tr>
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</table>
Symbols

$N_j$  shape function
$n_n$  number of nodes
$n_{en}$  number of space-time element nodes
$n_{quad}$  number of quadrature points
$n_{sd}$  number of space dimensions
$n_{st}$  number of space-time intervals
$p$  pressure
$p'$  pressure perturbation
$P_n$  boundary of space-time slab
$Q^*$  reference element domain
$Q_n$  space-time slab
$R_1$  inner cylinder radius
$R_2$  outer cylinder radius
$R_i$  radius of a particle
$R_{pl}$  average platelet radius
$Re_1$  Reynolds number (inner cylinder)
$Re_2$  Reynolds number (outer cylinder)
$S$  free surface percentage
$S_i$  source term for component $i$
$T$  absolute temperature
$t$  time
$t_{act}$  characteristic time for platelet activation
$U$  characteristic velocity
$u$  value to be transported in advection-diffusion-equation
$u'$  velocity perturbation
$u^h$  finite-element trial function
$u_\theta$  azimuthal velocity component
$u_r$  radial velocity component
$u_z$  axial velocity component
$w^h$  finite-element weighting function
$w^j$  quadrature weights
$w_j$  agonist-specific weight of agonist $j$
$\text{Act}$  platelet activation parameter
$\text{Agg}$  platelet aggregation indicator
$\text{Hct}$  hematocrit
$\text{Pe}$  mesh Peclet number
$\text{Ta}$  Taylor number
$\text{Ws}$  Weissenberg number
Appendix A

XNS

XNS is a massively parallel finite-element flow simulation program that is currently in development at the chair for computational analysis of technical systems (CATS) at RWTH Aachen university. It has a built-in representation of the advection-diffusion-reaction equations with a choice of either semi-discrete or space-time finite-element discretization schemes. XNS assembles the stiffness matrices and right hand side vectors for the complementary partitions of the computational domain in a block sparse row (BSR) storage and uses an implementation of the (restarted) generalized minimum residual method (GMRES) introduced by Saad and Schultz \cite{46} to solve the sparse linear system.

The original XNS code was branched and extended such that it is possible to solve systems of coupled advection-diffusion-reaction equations with reactive wall boundaries in space-time.

A.1 General setup

Solving the advection-diffusion-reaction equations in XNS can be done by setting the advection parameter in xns.in. Make sure that the parameter laplace is set to off (which is by default), because the Laplace variant ignores the advective term.

\begin{verbatim}
    advection
    laplace off
\end{verbatim}

If a steady case is simulated the time discretization is activated by setting

\begin{verbatim}
    steady on
\end{verbatim}

which is off by default. The ambient velocity is usually set by a mathematical expression:

\begin{verbatim}
    ambient <exp_x> <exp_y> (<exp_z>)
\end{verbatim}

where <exp_x>, <exp_y> and <exp_z> are expressions that describe the desired velocity field. If the ambient velocity cannot be (easily) formulated by expression it may be convenient to use a pre-computed velocity field as input data. This can be done by pointing the daux variable in XNS to a file containing the velocity field and the pressure u,v(w),p. For steady cases set ambient steady and for unsteady cases ambient unsteady.

\begin{verbatim}
    daux <filename>
    ambient <steady/unsteady>
\end{verbatim}
A.1 General setup

Note that in an unsteady case it is necessary to have a (space-time) record for each timestep that has to be computed. To avoid complications make sure that the velocity field is pre-computed such that two subsequent time steps in the record file have a temporal difference of the same \( dt \) as is specified in your advection-diffusion-reaction case and the number of records is greater or equal to the number of time steps \( n_{ts} \) that are to be solved. The pressure data in the file specified in \( \text{daux} \) is for technical reasons required but ignored in the simulation.

The solver was extended to solve systems of advection-diffusion-reaction equations simultaneously. Therefore it is necessary to specify the number of equations to be solved. This is done by setting the number of degrees of freedom per node via

\[
\text{ndf} \ <n>
\]

XNS is designed as a Navier-Stokes flow solver but is also capable of solving other PDEs like advection-diffusion-reaction equations. Because the viscosity in the Navier-Stokes equations corresponds to the diffusivity coefficient in the advection-diffusion-reaction equations, the latter is defined by setting the variable \text{viscosity} in the material definition. Material group \( i \) corresponds to the \( i \)-th DOF. To set the diffusivity coefficient for a certain DOF, simply define a new material group as

\[
\text{material} \ <i> \ \text{viscosity} \ <\text{diffusivity}>
\]

Note that once you try to solve a coupled system it is inevitable to specify a diffusivity for each DOF. The diffusivity cannot be set by expression in the current (November 26, 2008) release of XNS, thus \( \text{diffusivity} \) has to be a constant value.

Initial conditions are set via the \text{initexp} parameter. For each DOF an expression specifies the initial field of values:

\[
\text{initexp} \ <i> \ <\text{exp}>
\]

The reaction term in the advection-diffusion-reaction equations corresponds to the body force term in the Navier-Stokes equations. The parameter \text{bodyexp} has to be set per degree of freedom:

\[
\text{bodyexp} \ <i> \ <\text{exp}>
\]

For the simulation of coupled systems a new syntax was implemented in ewdlex to specify expressions that depend on a DOF. To obtain a DOFs value simply type \([i]\), where \( i \) is the number of the desired DOF. Note that usually several nonlinear iterations are needed to obtain good results in case of coupled equations. The number of nonlinear iterations can be adjusted by setting the parameter \text{nit}:

\[
\text{nit} \ <n>
\]
Appendix A XNS

A.1.1 Using the model

To use the model presented in chapter 2 the following line has to be added:

```
platelet_model adr_1 <Act> <Agg>
```

where `<Act>` and `<Agg>` are the dimensionless numbers Act and Agg, respectively. This tells the solver to include the coupling reaction terms. Those can also be defined by the bodyexp-function described before but parsing and evaluating expressions consumes a lot of computational time. For large simulations the hardcoded variant may be much more efficient.

A.2 Boundary conditions

The Dirichlet and Neumann-type boundary conditions have to be imposed on disjoint subsets of the boundary \( \Omega = \Omega^D \cup \Omega^N \) for simulation. In XNS per default homogenous Neumann BCs are imposed if nothing else is prescribed. To identify the different regions of the boundary the input mesh should have reference node groups specified.

A.2.1 Dirichlet BCs

To constrain any DOF in XNS the `rngdset` parameter needs to be set.

```
rngdset <rng> <i> <2> ... <ndof>
```

If \( i \geq 0, i=1,...,\text{ndof} \) then the \( i \)-th DOF is constrained. Once the DOF is constrained `rngdexp` can be used to prescribe the boundary condition by expression for a given RNG and DOF.

```
rngdexp <rng> <dof> <exp>
```

**Mathematical formulation:**

\[
u^{(i)} = g(x, t) \quad \text{on } \partial \Omega^D
\]

**XNS input:**

```
rngdset <rng> <i>
rngdexp <rng> <i> <g>
```

A.2.2 Model specific: Reactive walls

To solve the model presented in section 2.2 it is necessary to specify the reactive wall flux boundary conditions (2.29-2.31). This can be done using the reactive input parameter for the wall RNG:

```
reactive <rng> <M> <k_rs> <k_as> <k_aa>
```

where \( <M>\) is \( M_\infty/[PLT]_\infty\), \( <k_rs>, <k_as> \) and \( <k_aa> \) are the lumped reaction rates \( k^*_{rs}, k^*_{as} \) and \( k^*_{aa} \) respectively.
Listing: Taylor-Couette XNS input

# mesh input (space-time hexahedral)
source minf
nen 16
nprmread on

# model parameters
advection
nsd 3
ndf 3
laplace off
steady off

# stabilization parameters
element_length supg
tau_momentum supg
tau_momentum_factor 1.0

# time-integration parameters
space-time
nts 3000
ntsbout 10
dt 0.1

# nonlinear iterations
nit 5

# GMRES solver parameters
maxinner 70
maxouter 2

# ambient velocity from pre-computed Taylor vortex flow
daux taylor.aux
ambient steady

# diffusivities
material 1 viscosity 8.1675e-6
material 2 viscosity 8.1675e-6
material 3 viscosity 2.57e-6

# initial concentrations
initexp 1 0.475
initexp 2 0.050
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initexp 3 0.000

# platelet model parameters
platelet_model adr_1 3.6 1.8e-3
reactive 13 0.0267 0.2e-3 0.21e-3 0.34e-3
reactive 14 0.0267 0.2e-3 0.21e-3 0.34e-3

A.3 Code validation

A.3.1 Gray-Scott model

The extended implementation of the XNS code for a reaction term coupled set of equations was validated using the Gray-Scott model [42]. The diffusion-reaction type model equations read as

\[
\begin{align*}
  u_t - D_1 \nabla^2 u &= -uv^2 + \gamma (1-u) \\
  v_t - D_2 \nabla^2 v &= +uv^2 - (\gamma + \kappa) v
\end{align*}
\]

(A.1) (A.2)

where the parameters were chosen conforming to [29] as \( \gamma = 0.024 \), \( \kappa = 0.06 \), \( D_1 = 8 \cdot 10^{-5} \) and \( D_2 = 4 \cdot 10^{-5} \). The initial concentrations are given as

\[
\begin{align*}
  u(x, y, 0) &= 1 - 2v(x, y, 0) \\
  v(x, y, 0) &= \begin{cases} 
  \frac{1}{4} \sin^2(4\pi x) \sin^2(4\pi y) & \text{if } 1 \leq x, y \leq 1.5 \\
  0 & \text{elsewhere.}
  \end{cases}
\end{align*}
\]

(A.3) (A.4)

The setting is a 100 \times 100 quadrilateral space-time mesh with homogenous Neumann BCs. The solution was computed for 10000 uniform time steps of \( \Delta t = 0.1 \) and shows a good agreement with solutions from literature (e.g. Hundsdorfer [29]).
A.3 Code validation

Figure A.1: Results: contour plot of solution $v$: top left: initial solution $t = 0$. top right: $t = 100$. bottom from left to right: $t = 200$, $t = 500$, $t = 1000$. 

xxi
Listing: Gray-Scott XNS input file

# mesh input (space-time quadrilateral)
source minf
nen 8

# model parameters
advection
nsd 2
ndf 2
laplace on
steady off

# time-integration parameters
space-time
nts 10000
ntsbout 100
dt 0.1

# nonlinear iterations
nit 5

# GMRES solver parameters
maxouter 2
maxinner 20

# diffusivities of different species
material 1 viscosity 8e-5
material 2 viscosity 4e-5

# reaction terms
bodyexp 1 (0.024*(1-[1])-[1]*sqr([2]))
bodyexp 2 (-0.084*[2]+[1]*sqr([2]))

# set initial concentration of species
initexp 1 (1-2*(sqr(0.5*sin(4*pi*x)*sin(4*pi*y)))*heaviside(x-1.0)
    *heaviside(1.5-x)*heaviside(y-1.0)*heaviside(1.5-y)))
initexp 2 (sqr(0.5*sin(4*pi*x)*sin(4*pi*y)))*heaviside(x-1.0)
    *heaviside(1.5-x)*heaviside(y-1.0)*heaviside(1.5-y))

# boundary conditions are homogenous Neumann (default)