The mechanical interaction between the red blood cells and the blood vessels

Theses of the PhD dissertation

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1. **INTRODUCTION**

Since my graduation at the university I have been working in a research group, which aimed to develop a numerical model for the analysis of damaged human blood vessels, i.e. a model, which is hoped to once help medical doctors to judge whether a damaged section of the blood vessel (e.g. an aneurysm, an adverse vasodilatation) needs to be operated on, and if so, with what urgency.

Originally my task was to perform laboratory analysis on the specimens taken from the wall of the vessel, to calculate material model parameters for numerical models based on my measurements. During my work I have come across the issue, which initiated and became the major topic of my research. The related scientific problems may give a vast amount of possible research topics for a long time.

The question posed by the medical doctors is as follows: *Is it possible by means of engineering models to estimate the forces exerted by the red blood cells afloat in the blood plasma in the human arteries on the endothelial cells covering the walls of the vessels acting as switch boards?* The doctors believe that a solution to this problem could render much help to the understanding of the physiological processes of the vessel wall, to a better description of the biomechanical-biological system controlling the behaviour of the vessel, since according to their observations the endothelial cells can control the mechanical behaviour of the vessel (contraction and dilatation) and certain chemical reactions be means of impulses due to such collisions.

In order to understand the abovementioned question from an engineering point of view, it is important to know that the arteries can be modelled as tubes with elastic walls, inside which the flowing fluid is represented by the blood plasma (with properties very close to those of water), and the cells of different size move in this plasma, including in the greatest number the red blood cells, which form a foundation of human life. We ought to know that the volume proportion of the cells in the plasma is considerable, i.e. we have to examine a densely concentrated fluid. The solid particles may collide with each other and the wall of the vessel during their motion, and the question is about how one can model such motion and calculate the value of the contact forces?

It is important to know that this problem of biomechanical origin has many similar counterparts in other fields of interests. A typical problem of this kind is the solid slurry rarefied with fluids transported in pipelines or the analysis of pneumatic material transport.

Considering all of the above mentioned I can formulate the aim of my dissertation: **I intend to answer the question to what kinds of modelling and in what way can one determine the influence of red blood cells afloat in human arteries on the vessel wall.**

In order to solve this problem I have performed as follows:

1. I performed laboratory measurements on specimens of vessel wall in order to determine the strength properties of the vessel wall. Several members of staff at the Budapest University of Technology and Economics deal with the simulation of brain aneurysms (sack-like vasodilatations), which makes it important to learn the modified properties of such adverse vessel sections. Naturally, to make a comparison, for this purpose we have to know the material properties of the healthy vessels as check data. One of my aims is to
determine material properties of both the adverse and the healthy vessels, which can be applied to computational models. Measurements on the material properties was necessary because I have not found any database regarding such vessels. It is the case because in several countries measurements on human tissues are prohibited by the law, and the scarce data collected with difficulty in the literature come from animal experiments.

2. During the numerical modelling I took into consideration the material properties of my own measurements to describe the elastic behaviour the vessel wall, therefore I can consider the material properties of the elastic tube in the coupled models.

3. I performed the numerical analysis both on my own continuum-based coupled and non-coupled vessel wall–blood flow models, and the discrete element models.

4. I carried out critical analysis on the numerical models used in practice for fluid mechanical analysis with respect to their extent of applicability to model the mechanical effects of red blood cells regarded as rigid flowing in the blood plasma. The presence of the red blood cells have not been considered so far, now I have done that. I model the red blood cells as rigid spheres in some of my models and with elastic material and shape close to reality in others. The inner wall of the lumen of the vessels (hollow inside) has so far been considered smooth, now I have modelled the protruding caps of the endothelial cells as well, in a range where it matters.

5. I performed computer simulations on the numerical models I regarded applicable for the calculation the impact forces of the red blood cells.

6. I set myself aim to simulate some phenomena known by doctors but not investigated numerically so far. Such phenomenon is the parallel orientation of the red blood cells in the arterioles (anterooms to the capillaries), and I have also investigated the important case when the diameter of the artery is so small that the red blood cells can pass through in a single file only (see the so-called bolus flow later).
2. RESEARCH METHODS AND RESULTS

2.1. LABORATORY MEASUREMENTS FOR THE DETERMINATION OF STRENGTH PARAMETERS OF THE VESSEL WALL

Let us consider the mechanical material model which we can use for our intended mechanical analysis of the vessel wall. It is often assumed about polymer-like – live or lifeless – materials with inner microstructure that they do not change their elementary volume due to external mechanical influences, that is (in the case of homogeneous isotropic material) their bulk modulus is approximately infinite and their Poisson’s ratio is 0.5. The material of the vessel wall can be considered of this kind.

Stresses in hyperelastic, rubber-like materials are obtained by derivation of a deformation energy function assumed as known. I determined material properties for the so-called Mooney–Rivlin model, which is one of the most widely used model in numerical software packages. The Mooney–Rivlin energy function applies deformation invariants \( I_1', I_2' \) and the condition \( I_3 = \lambda_1^2 \lambda_2^2 \lambda_3^2 = 1 \). The model has variants with two, three, five, or more parameters, too. Let us consider the energy function related to the variants with two, three, and five parameters without much detail. In the case of five parameters, the Mooney–Rivlin deformation energy function takes the form of

\[
\Psi = c_1(I_1' - 3) + c_2(I_2' - 3) + c_3((I_1' - 3)^2 + c_4(I_1' - 3)(I_2' - 3) + c_5(I_2' - 3)^2.
\]

where \( I_1' \) is the first deviatory deformation invariant, \( I_2' \) is the second deviatory deformation invariant, \( c_1, c_2, c_3, c_4, c_5 \) are parameters characterizing the deviatory deformation of the material. The three-parameter variant of the Mooney–Rivlin models differs from this only as it contains material constants \( c_1, c_2, c_4 \) in the equation above, while the two-parameter variant contains \( c_1, c_2 \) only.

It is essential for the numerical analysis of human artery walls to have at least an approximate knowledge on the material behaviour of the vessel wall. In order to reach this goal, laboratory measurements have been undertaken for several years in the Institute of Human Physiology and Clinical Experimental Research of the Semmelweis University. I joined this series of measurements, too. We have taken the specimens of the vessel wall from patients under operations, and from brain vessels extracted from cadavers (deceased patients), and then we have measured the stress-strain curves of the material of the vessel wall in one-dimensional and two-dimensional tensile tests.

We cut 3 mm wide lengthwise and circumferential stripes out of the brain arteries (vessels of type *internal carotid artery*) obtained from cadavers for the purposes of the uniaxial tests and 8-by-8 mm large square-shaped specimens parallel to the above directions for the biaxial tests. The specimens were gradually pulled by a device equipped with strain gauges (fixed at both ends for uniaxial tests and fixed at all four sides for the biaxial tests), while the pulling force was digitally recorded (Fig. 1).

During the processing of the measurement data, we have considered the original position of the specimens in the artery, basically in order to examine the inhomogeneous and anisotropic character of the material behaviour as accurately as possible.
Figure 1. Biaxial laboratory measure device

The main parts of the biaxial device and the block chart are shown on the left and on the right, respectively. The specimen holders (H) are displayed with the two strain gauge (SG) attached. The two pairs of holders are placed perpendicular to each other. The output of the gauges is lead to a two-channel force measuring device, and the signals are transmitted to a PC by a multilab card. Displacements of the screws are actuated by 4 motors (SM), and the motions are transmitted to the PC by the multilab card and the SM control unit.

It is a common property of the curves obtained that the initial line with small elastic modulus is followed by a steeper curve with an elastic modulus multiple of the initial one. Dividing the curves in two parts approximately linear sections are obtained, hence separate moduli of elasticity can be determined for each section. I have evaluated the measurements on the 12 specimens of internal carotid artery and determined the piecewise moduli of elasticity. During these measurements I have calculated moduli of elasticity of lengthwise, circumferential, and square-shaped (for the biaxial tests) specimens for all artery sections, therefore I was able to evaluate a total of 46 valid measurement data.

By means of the stress-strain curves calculated from my measurements on internal carotid arteries, I determined the hyperelastic Mooney–Rivlin material parameters required for the numerical analysis. By calculating the material properties I did not purely aim to provide data for my own research, but to make the foundations of a database which can be utilized by both medical doctors and engineers, and expanded in the future, too. Precisely for this purpose I have separately evaluated each specimen, and then tried to generalize the results. In the case of measurements on internal carotid artery used as a control group, I found the biaxial results particularly valuable. Plotting all curves obtained from biaxial measurements we can only deduce that a softer and a harder type of material can be distinguished. I fitted Mooney–Rivlin curves for all measurement series on internal carotid artery, and also on measurements I judged to be belonging to the softer and the harder types of material separately. For each measurement I considered the number of parameters (2, 3, or 5) in a way to get an acceptable approximation. The results are summarized in Table 1 without details, together with the averaged maximal stresses and strains related to the first damaged states, which are regarded as failure.
Following my measurements on the walls of healthy arteries I dealt with the examination of aneurysms (adverse vasodilatations). As I have mentioned before, I joined a series of measurements running for years at the Institute of Human Physiology and Clinical Experimental Research of the Semmelweis University. I took over the measurement series from Dr. Gábor Raffai, who performed measurements under the supervision of Dr. Emil Monos. He cut stripes out of the aneurysms parallel to the imaginary axis (meridional) and perpendicular ring-like direction (circumferential) for the uniaxial tests. I have performed the procedure shown for the internal carotid artery now for the total of 91 uniaxial measurement results, too. During this I determined stress-strain curves, and determined for each specimen whether the 3-parameter or the 5-parameter variant of the Mooney–Rivlin model approximates the diagrams more precisely. Since I had a significantly larger amount of measurement data were at my disposal, I examined differences with respect to gender and orientation. I formed a total of 9 groups: all together, males and females separately, circumferential (perpendicular to the main axis of the aneurysm) and meridional (approximately in the main axis of the aneurysm) separately, and also the cases of circumferential female, circumferential male, meridional female, and meridional male. Unfortunately, the data were insufficient to distinguish on the basis of pathological history. Distinctly visible difference is observable after averaging samples from women and men. I found that samples from men are harder: they get damaged by lower strains but higher stresses. This symptom remains, if we examine women and men belonging to the circumferential class, as well as (but less characteristically) do the same in the meridional class. I did not show significant deviation between classes circumferential and meridional. In Table 2 I have summarized the Mooney–Rivlin material constants obtained by the grouping of aneurysms, together with the averaged maximal stresses and strains related to the first damage regarded as failure.

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Table 1: Hyperelastic material model parameters obtained from averaging specimens of internal carotid artery (ICA), and the maximal stresses and strains related to the first irreversible damage.

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<td>187800</td>
<td>196000</td>
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<td>58000</td>
<td>431500±69420</td>
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<td>ANEURYSM female</td>
<td>-101600</td>
<td>154200</td>
<td>118900</td>
<td>-58000</td>
<td>58000</td>
<td>416200±68570</td>
<td>0,6995±0,0767</td>
</tr>
<tr>
<td>ANEURYSM male</td>
<td>-104200</td>
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<td>-58000</td>
<td>58000</td>
<td>524200±151300</td>
<td>0,5928±0,1154</td>
</tr>
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Table 2: Hyperelastic material model parameters of aneurysms – obtained by averaging and grouping, and the maximal stresses and strains related to the first irreversible damage.
2.2. NUMERICAL MODELS OF RED BLOOD CELLS IN THE BLOOD FLOW ON CONTINUUM-MECHANICAL BASIS

After the determination of the material properties of the vessel wall, the next step is the performing the numerical analysis for the aims set in the introduction. To achieve this I found the pure continuum-based modelling the appropriate choice. I examined the limits of applicability of such modelling (models complying with the assumptions of continuum mechanics). Since in the dissertation my aim was to model the influence of the red blood cells carried by the blood flow on the walls of human arteries, it follows that I was to use fluid mechanics software packages which are able to consider the influence of particles carried in a flowing medium. I examined what possible choices are available in continuum mechanics for the computational fluid dynamics (CFD) modelling of particles dispersed in a fluid in a tube. I found the Lagrange-based particle tracking multiphase modelling, or the so-called particle transport method in short form, appropriate for the analysis of solid particles in a continuum fluid medium. I intended to explore its potentials and limitations.

2.2.1. CALCULATIONS BASED ON THE MODEL OF THE RIGID VESSEL WALL

In my numerical calculations the particle transport modelling can only regard particles as spheres, therefore I chose the radius of the equivalent sphere \( r_{\text{red}} \approx 2.78\mu\text{m} \). In this case the volume of the sphere is identical to that of the red blood cell, while the surface of special shape of the red blood cells is not identical to that of the equivalent sphere. Therefore it is recommended to bridge the difference by applying a modifying shape factor of 1.44, which was duly considered in my fluid dynamics analysis. Note that though the resistance in the fluid medium is direction-dependant due to the shape of the red blood cells, it cannot be taken into consideration in this model. It is due to the fact that in the particle transport model the motion of the particles is represented by their centres of mass and we cannot monitor their orientation with respect to the direction of the flow.

During the calculations my fundamental assumption was that purely continuum-based analysis can only be applied to vessels of larger diameter, where the diameter of the red blood cells is significantly smaller (by 2 or 3 orders of magnitude) than that of the vessel. Since the modelling of the blood flow has not taken into consideration any cell components so far, I have investigated the influence of the concentration of particles (see Fig. 2). Firstly, I performed numerical analysis on the blood flow in vessels in the range of internal carotid artery. In the analysis to make comparison easier I took the velocity at a constant value of 35 cm/s (physiologically realistic value), and the pulsing load was neglected. Also in favour of comparison (referring to Zamir [2005]) I assumed laminar flow. I run the simulations on an idealized curved section of vessel of diameter of 3 mm using the software package ANSYS 11.0.
I have also examined the influence of the diameter of the red blood cells relative to that of the artery (see Fig. 3 for result plotted in a logarithmic scale). The value of the diameter in the analysis was taken in unit of mm as 0.006; 0.03; 0.06; 0.3; 0.6; 3; 15, and 30, respectively. The smallest value of 0.006 mm in this series represents capillaries with diameter in the range of that of the red blood cells, while the largest value of 30 mm belongs to the upper limit of largest vessel in the human body, the abdominal aorta.

2.2.2. CALCULATION BASED ON THE MODEL OF THE HYPERELASTIC VESSEL WALL

My next task was to create the model of the blood and the vessel wall with multiple couplings. On the one hand, the fluid (i.e. the blood) and the particles carried in it (red blood cells) mutually influence one another (see previous section, also in the case of the rigid wall), and on the other hand, due to the pulsing of the blood plasma, the motion of the vessel wall encircling the lumen of the blood reacts on the flowing field. Thus the so-called multiply coupled ('back and forth') modelling is doubly present in the problem I analyse. During the modelling the two ends of the artery section were fixed for brevity, and the tube was surrounded by elastic embedding representing brain tissues.

I carried out numerical analysis of blood flow in vessels in the range of internal carotid artery because this is the range of which I possess material properties. I determined these properties from the vessel models created using the averaged material properties of my biaxial tests (see
the first row in Table 1). Keeping the geometry created for the rigid wall analysis as the fluid space, I supplemented the model with an encircling ring of width 0.6 mm representing the material of the vessel wall. I performed fluid dynamics simulations on the fluid contained in the lumen of the vessel as before, and a solid mechanics finite element analysis on the encircling ring, and the two were coupled. In each time step the output of the fluid dynamics simulation in the tube with rigid wall was applied as loads on the encircling ring of hyperelastic material. The displacements arising in that tube were applied then to the fluid field in the next time step in such a way that the fluid space was modified with those displacements. The input fluid flow and the particles representing the red blood cells were the same as in the case of the rigid wall model of idealized geometry with diameter of 3 mm and concentration of 40-50% (the physiologically realistic value). I did not elaborate the effects of the elastic supports applied around the tube of the artery since this topic is investigated by another member of our department, Ferenc Nasztanovics.

Following the numerical simulations on the idealized geometry, I have performed simulations with finite element software package ANSYS 11.0 on real geometry as well – on a section of vessel containing a real brain aneurysm. The geometry and finite element mesh I used were obtained from Ádám Ugron, a member of the Department of Hydrodynamic Systems at BUTE, who deals with the simulations of fluid dynamical conditions of real brain aneurysms. Again in the numerical simulations I applied the hyperelastic material properties I gained from my laboratory measurements. I compared two cases. In the first case I applied the Mooney–Rivlin material parameters obtained by fitting a curve to the averaging of the healthy control arteries (internal carotid artery) to the entire vessel (including the aneurysm), see the first row in Table 1. In the second case the above mentioned parameters related to the general healthy arteries were exclusively applied to the parent arteries of the model and the aneurysm itself was modelled with Mooney–Rivlin material parameters obtained from the averaged curves of measurements on the aneurysms, see the first row in Table 2. Since geometric dimensions of this real model were in direct correspondence with my idealized tube with diameter of 3 mm, the velocity of the blood was taken at a value of 0.35 m/s.

Figure 4: von Mises stresses in an aneurysm with real geometry
a) the entire vessel wall as internal carotid artery b) parent artery as internal carotid artery, and dilated section as aneurysm
I found significant difference in stress values between the case of modelling the aneurysm with Mooney–Rivlin parameters of healthy vessels and the case of Mooney–Rivlin parameters of real aneurysms (see the von Mises stresses in Fig. 4 and also the principal stresses in Table 3).

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<td>0.1</td>
<td>-0.4</td>
</tr>
<tr>
<td>Dilatation as aneurysm</td>
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<td>4</td>
<td>1.45</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

*Table 3: Maximal stresses in the aneurysm bag (pr.=principal)*

2.3. NUMERICAL MODEL OF THE FLOW OF RED BLOOD CELLS IN CAPILLARIES

As we go towards arteries with less and less diameter, the consideration of dimensions of red blood cells becomes more and more important. The procedure shown in the previous section can only be applied to arteries with diameter at least of the range of mm. Let us pass on to a smaller range (the missing interval will be dealt with later), and see what happens in the extreme case of the smallest vessels, the so-called capillaries. It may also happen that red blood cells can only travel in a single file forming so-called boluses with the plasma, see Fig. 5. Their diameter may reach or even exceed that of the capillaries.

*Figure 5: Bolus flow in capillaries: a sketch (Monos [2001])*

The biconcave shape of the red blood cells plays a significant role in the bolus flow mentioned above. Since my primary aim is to model the actions on the wall, i.e. on the endothelial cells acting as switch boards, this phenomenon should be paid special attention. In this range the working of the endothelial cells are determined by the changing fluid field around the file of the cells and the friction between the cells and the wall, and not the dynamic impact of the collision of the particles to the wall.

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2.3.1. RED BLOOD CELLS MOVING AS RIGID BODIES IN VESSELS AS RIGID TUBES WITH REMESHING

In the case of so-called FSI (fluid structure interaction) problems it may happen quite often that due to large displacements the large deformations of the finite element mesh cause the computation to halt. As the primary aim is to examine the motion of the red blood cells, i.e. how a red blood cell regarded as a rigid body moves in a tube (artery) regarded as rigid body, the large displacements of the red blood cells makes it necessary to re-mesh the fluid field time to time.

In the following I present the method I developed for the simulation of rigid body motion of red blood cells based on the works by Panhuber and Bárdossy [2010]. In my model the diameter of the artery is 10 \( \mu \text{m} \), the diameter of the red blood cell is 7.58 \( \mu \text{m} \), its largest width
is 2.38 μm, and its width in the middle is 1.2 μm. As both the wall of the tube and the red blood cell are rigid, only the mesh of the purely fluid dynamics simulation needs to be created. Thus the red blood cell can be regarded as holes within the fluid field, which moves as a rigid boundary. The calculation requires Newton's two laws of motion defining two states: translational motion and rotary motion. In order to simulate the motion of red blood cells in the fluid space, we have to calculate the displacements and the new positions due to the forces acting on them in each time step, and relocate them to their new position. We can proceed with it until the mesh suffers so large deformations that a re-meshing becomes necessary. The threshold I choose for re-meshing is 5 degrees, i.e. when in any of the elements of the mesh an angle falls below 5 degrees, the process stops temporarily, the geometry data are transferred to the mesh generator module, which performs steps I have predefined whenever it is called for re-meshing the geometry. The basis of the algorithm describing the translation and the rotation is as follows. For the new value of the translation and the rotation we can formulate that

\[F_{\text{Folyadék}} + m_{\text{VVS}} \left( \frac{v_{\text{VVS},i}}{t_{\text{Step}}} + \frac{\xi_{\text{VVS},i}}{t_{\text{Step}}} \right) \]  
and \[M_{0,\text{Folyadék}} + I_{0,\text{VVS}} \cdot \left( \frac{\omega_{\text{VVS},i}}{t_{\text{Step}}} + \frac{\phi_{\text{VVS},i}}{t_{\text{Step}}^2} \right) \]  

where \(m_{\text{VVS}}\) is the mass of the red blood cell, \(v_{\text{VVS}}\) is its velocity, \(\xi_{\text{VVS}}\) is its displacement in the given direction, \(F_{\text{Folyadék}}\) is the force exerted by the fluid, \(t_{\text{Step}}\) is the time step applied in the numerical simulation, \(M_{0,\text{Folyadék}}\) is the moment exerted by the fluid on the red blood cell, \(I_{0,\text{VVS}}\) is the inertial moment of the red blood cell, and \(\omega_{\text{VVS}}\) is the angular velocity of the red blood cell.

I examined two cases: in the first case a single red blood cell is placed in the tube with its middle plane perpendicular to the direction of the flow, in the second case two red blood cells are placed in the tube (at a distance of 10 μm from each other) again with perpendicular orientation. I determined that during the simulation the red blood cell gradually takes a velocity close to that of the fluid flow. It can be observed in the simulation of two bodies that their motion mutually influences each other. This “jostling” will cease after a while, and both bodies together take their final, permanent velocities.

Let's make a little looking out in the future. In my purposes occurs the examination of flowing in capillaries of that red blood cells, which ones travels on the slant in a special, abnormal case. I made a third type numerical model, when a single red blood cell is applied now rotated around one of the axes by 45 degrees in the tube. The investigation of this case is be a part of my further plans.

I also obtained an interesting result regarding the case of the cell in an oblique position. Further to the phenomenon known by means of the translational motions, namely that it takes a velocity close to that of the fluid, I observed that its rotation is insignificant compared to its translational motion. During the translation of 9 μm in z direction (the axis of the artery) the maximal rotation around the y axis is only 0.004 radians (0.23 degrees), and it seems to stabilize.

The phenomenon exhibited by means of my models, namely that the red blood cells move with the flow with insignificant rotation relative to their translational motion, is called bolus flow by physiologists. This has not been analysed numerically so far to my best knowledge.
Fig. 6 shows the shear stresses along the wall around cells via the example of the two cells in perpendicular direction.

![Image showing shear stresses](image)

**Figure 6:** a) Two red blood cells in perpendicular direction, and b) the stresses arising in the wall in its vicinity.

### 2.3.2. RED BLOOD CELL MOVING AS AN ELASTIC BODY IN A VESSEL WITH ELASTIC WALL

In the case when one cannot be satisfied with the simulation of the red blood cells as rigid bodies in a rigid tube, the fluid dynamics software I know cannot provide re-meshing and elastic walls together. On the other hand, if our aim is to model the material of the vessel wall and to calculate the stresses and strains in it, and also to model the deformations of the red blood cells, then the FSI modelling gains a new perspective. Now the aim is to get the solid mechanical solver and the fluid dynamics software communicate with each other instead of the fluid dynamics solver and the re-meshing module. In the present case forces arising from the fluid generate stresses and strains in the vessel wall and the red blood cell, which then reacts the fluid field. Coupling between the solid and the fluid phases is to be defined in this way.

In the case of the model simulating the rigid red blood cell in the rigid tube I had to apply a long tube in order to set the time step sufficiently large to numerically stabilize the model. However, in this case there is no need for such long input and output sections as the red blood cell will not translate. The geometry is identical to the one applied in the previous case, except that the length of the tube is smaller: a single red blood cell with diameter of 7.58 μm, width at the rim of 2.38 μm, and width in the middle of 1.2 μm is placed in the middle of an artery section with length of 40 μm and diameter of 10 μm. The fluid space is surrounded by a vessel wall necessary for solid mechanics computations with thickness of 1.5 μm. Since in this range the vessel walls are almost exclusively built up with endothelial cells, the magnitude of the thickness mentioned above is appropriate. Unfortunately, in the literature I could not find any reliable data for the modulus of elasticity of the endothelial cells taken from human capillaries, therefore I assumed the value of 5000 Pa realistic based on the articles I found, and performed the computations with this value (values in the literature vary...
between 400 Pa and 8000 Pa). While in the case of the previous model the red blood cell was represented by a hole with physical properties, now it is fitted with real volume and material properties. I set the modulus of elasticity of the red blood cell at $10^5$ Pa ([Hochmuth](#)), and did not deal with the effects of elastic support.

I applied an input fluid flow with a constant maximal velocity $v_{\text{max}} = 0.0003 \text{ m/s}$ as a loading, since the pulsing of the heart is practically non-perceptible in the domain of the capillaries, nevertheless it is reasonable to keep the parabolic velocity profile. It is taken as:

$$v = v_{\text{max}} \left(1 - \left(\frac{r}{R_{\text{max}}} \right)^2 \right)$$

(3)

where $r$ is the distance measured from the axis of the tube, and $R_{\text{max}} = 5 \mu\text{m}$ denotes the inner radius of the tube. As I have elaborated in the case of the previous model regarding rigid body motion, I created an algorithm, which in each time step calculates the resultant of the forces acting on the red blood cells, then their velocity, and the magnitude of the rigid body displacements during the time step, and then relocates the red blood cells accordingly. In the ANSYS CFX 11.0 software package the coupled fluid dynamics–solid mechanics problem cannot incorporate re-meshing (the possibility of loading of a new mesh is not supported), therefore to avoid this problem, I attached the coordinate system of my analysis to the red blood cell instead of the tube. By means of this idea the red blood cell becomes stationary while the surrounding wall moves in opposite direction to the input velocity profile at precisely the same velocity as that which I have calculated for the red blood cell in the previous method. Naturally, the velocity of the wall – in opposite direction to the flow – was recalculated in each time step. Now as the wall moves instead of the red blood cell, the velocity profile of the input fluid flow needs to be modified (see Fig. 7):

$$v = v_{\text{max}} \left(1 - \left(\frac{r}{R_{\text{max}}} \right)^2 \right) - v_{\text{wall}} ,$$

(4)

where $v_{\text{wall}}$ is the velocity of the wall, also recalculated in each time step.

![Figure 7: Plot of velocity profiles according to Eqs. (3) and (4).](#)

The maximal and minimal von Mises stresses arising in the vessel wall together with the principal stresses are summarized in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>maximum [Pa]</th>
<th>minimum [Pa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Mises stress</td>
<td>2.50E-04</td>
<td>9.35E-08</td>
</tr>
<tr>
<td>1st principal stress</td>
<td>1.23E-02</td>
<td>-1.17E-02</td>
</tr>
<tr>
<td>2nd principal stress</td>
<td>1.05E-02</td>
<td>-1.21E-02</td>
</tr>
<tr>
<td>3rd principal stress</td>
<td>8.78E-03</td>
<td>-1.38E-02</td>
</tr>
</tbody>
</table>

*Table 4: Maximal stresses arising in the vicinity of the red blood cell*
In the last two sections I have shown the possible ways of analysing arteries with diameter at least 50 to 100 times larger than those of the red blood cells as well as the case when they move in a single file in capillaries with approximately the same diameter. I have not elaborated the interval which lies between the two. Let us now consider the range of the arteries which is between the domains shown in the previous sections, i.e. where the diameter of the vessel is smaller than the magnitude of $mm$ and the particle transport modelling is not applicable any longer, and at the same time the diameter of the vessel is yet several multiple of that of the red blood cell, i.e. the finite volumes based method requires an unreasonable large number of elements. The analysis of a single red blood cell would require powerful computers. If one wishes to model the uniform flow of several tens or hundreds of red blood cells in the plasma, then it is necessary to switch from finite element modelling to the so-called discrete element modelling.

### 2.4.1. COUPLED DISCRETE ELEMENT MODELING

One of the new trends of discrete element modelling couples the mechanical computations of particles moving in the three-dimensional domain (discrete element software) with a ‘traditional’ Computational Fluid Dynamics (CFD) algorithm. The coupling is bidirectional. Unfortunately, our department has no access to a software package that incorporates the coupled model mentioned above for financial reasons, though I attended courses where I had the opportunity to work on such models and to explore the limits of their applicability. Based on my numerical simulations I have come to the conclusion that in order to obtain acceptable results in the coupled model, the fluid cell (hexahedron element) should be at least five times larger than the red blood cell contained in it, and the fluid space should be divided into at least five cells along its diameter. It means that this method can be applied to the analysis of arterioles with diameter 25 times larger than that of the red blood cells. It corresponds to arterioles with diameter of 150 $\mu m$ as a limit one can achieve.

### 2.4.2. TRADITIONAL DISCRETE ELEMENT MODELING

Let us consider what happens outside the domain of coupled modelling mentioned above, when the red blood cell is larger than one twenty-fifth of the diameter of the vessel. We need a model with which we can at least approximately simulate the phenomena in question. The endothelial cells that form the inner wall of the vessel have inner stiffness, and during the collision of the red blood cells with the wall – as a consequence of the forces on the endothelial cell wall – they transmit signals via the cellular switch structures. These signals fundamentally determine the biochemical response and reactions of the artery wall. I modelled these switch structures with five peduncles for each endothelial cell. Considering all these circumstances I applied a purely discrete element method for the analysis of this domain of arterioles. In purely discrete element modelling both the red blood cells and the blood plasma are modelled with particles. If we intend to model the continuum phase with fine particles filling up the entire fluid space, the chance stands that the vaulting of the particles...
may lead to false, useless results. This is the case even if we radically decrease the number of particles representing the continuum, countable number of discrete particles can never be fully equivalent to the continuum. Thus I decided to consider the approximate effects of the continuum phase with the help of several particles scattered in the domain. The scattered particles do not behave as a fluid, therefore some effects of the fluid (e.g. the shear stresses in the wall) cannot be calculated in this model. However, it can approximately show the phenomenon that the fluid (i.e. the particles representing the fluid) pushes the red blood cells ahead, and how the motion of the red blood cells reacts on the fluid. The extra pressure arising due to the collision of the red blood cells can also be modelled.

During their flow along the vessel the red blood cells turn in the direction of the flow with their axis – in vessels larger than capillaries. In order to verify this phenomenon I performed a numerical simulation in a straight tube surrounded by endothelial cells for a single red blood cell where the diameter of the red blood cell is half/third of that of the vessel. The small particles representing the blood plasma can reflect the effects of the fluid only with respect to their velocity distribution and the appropriate choice of the density. I applied a parabolic profile for the velocity distribution. I determined the density of the particles considering the porosity in a way that the total mass of the particles in a unit volume is identical to that of the blood plasma in the same unit volume. Fig. 8 shows the displacement of the red blood cell in a series of characteristic snapshots. It is easy to see that a red blood cell with axis perpendicular to the direction of the flow turns into the flow in the case of the conditions above.

**Figure 8: Discrete element simulation of the flow**

Once I could demonstrate the phenomenon that a single red blood cell turns into the direction of the flow, it became obvious that collision between the red blood cells and the endothelial cells can happen with the highest probability at the turns or bifurcations of the vessel in this range (due to the occurrence of axial flow).

**Fig. 9** shows a model capable of simulating a bifurcation. I introduced endothelial cells only in the vicinity of the bifurcation, while I applied a plain rigid wall in the preceding straight section. We have ability to monitor various effects caused by collisions. We are primarily interested in the stresses in the endothelial cells, and also in calculating the forces in the peduncles acting as the switch structures, since they are responsible for transmitting the information. In this model the diameter of the tube is approximately identical to that of the endothelial cells (17 μm approx.). In this range the realistic velocity of the flow is 0.8-1.6 mm/s and the simulation shows an approximately 2-3 Pa extra stress arising from the collisions.

**Figure 9:** Model for the simulation of a bifurcation and a typical location for the measuring of the stresses at the switch structures (peduncles) denoted by a blue circle.
CONCLUSIONS AND THE THESES OF THE DISSERTATION

The conclusions of the results of my research are summarized in five theses with fullness of details in accordance with the request of that content:

I. Thesis [1, 3, 4, 5, 6, 7, 9]

a) I performed uniaxial and biaxial stretching measurements on carotid interna type arteries obtained from interventions and from cadavers, by means of which I determined the characteristic stress-strain curves of the artery wall resulting from stretching force. On the basis of the stress-strain curves I developed the bilinear elastic and the more parametric hyperelastic Mooney–Rivlin constitutive material model of the artery wall for the period before damage. I created the basis of a database for medical purposes by performing the statistical investigation of the received results. In the direction of cutting-out I did not show significant deviation. Based on the measurements I concluded that the type of artery under examination can be premordially characterized by a soft and a brittle material type. My Mooney–Rivlin material parameters and other data (maximal stresses and strains) obtained from arteries can be used as fundamental tools for further numerical examination of human arteries.

b) Based on the measurements I determined the characteristic stress-strain diagrams resulting from stretching forces of human cerebral aneurysms. Based upon these findings I developed the multi-parametric hyperelastic Mooney–Rivlin constitutive material model of this type of abnormal arterial wall related to the period before the damage. I created the basis of a medical database, and for each of the measurement data I determined whether the 3-parametric or the 5-parametric model is more suitable to describe. By performing the statistical investigation of the received results I established that characteristic divergences appear depending on the gender, however I did not find evident difference as a function of the cutting direction. I proved that the tissue samples obtained from males are more brittle in all sample categories: they deteriorate at shorter stretching and at higher values of stresses than the tissue samples of females.

II. Thesis [3, 4, 8, 9]

a) I performed a parameter analysis on a model having rigid walls to simulate arteries of carotid interna type by the help of the so called particle tracking method by stationary flow, and I justified with numerical simulations that the consideration of the cellular elements transported in blood has considerable significance. In the case of fixed geometry (3 mm diameter of tube) and particle diameter (5.56 μm) I investigated the concentration with particles between 0% and 95% and I established that the value of the pressure gradient at 95% concentration is nearly the double of the value at 0% concentration. In the real physiological domain – 40-50% concentration – the value of pressure gradient is 35% higher than those in models applied by researchers so far, where the presence of cellular elements was ignored. I determined that a similar occurrence can be observed in the case of redundancy stresses in the wall caused by collisions of red blood cells. I determined the value of redundancy stresses in the wall caused by collisions of red blood cells. I determined that the maximal shear stresses in the wall have nearly the same values independently from the concentration in the case of arteries of carotid interna type.
I performed a parameter analysis on the same rigid wall type model – with particle tracking method by stationary flow – to investigate the influence of blood having physiologically real concentration in terms of different diameters of arteries. I determined that the results under the domain of magnitude of \( \text{mm} \) are no longer acceptable. Conversely, above the domain of magnitude of \( \text{mm} \) these redundancy stresses can be realistically calculated and they are proportional to input speed.

b) I also performed the previously mentioned investigations as coupled simulations on a model having elastic walls to simulate arteries of carotid interna type by the help of the so called particle tracking method, in which the hyperelastic Mooney-Rivlin material constants of the arteries of average carotid interna type were applied as material parameters. By the comparison of the tube having rigid walls (not coupled model) with the tube having elastic walls (coupled model) I proved that unambiguous decrease is observable in pressure gradient while it has no significant influence on shear stresses in the arterial wall.

c) I performed a numerical simulation of blood circulating in a real diseased arterial segment (including aneurysm) of dimension in the range of arteries of carotid interna type defined with Mooney–Rivlin material model with continuum based particle transport method by stationary flow. I proved that application of my material constants derived from the measurements performed on aneurysms yields significantly higher stresses compared to the application of material constants derived from the samples of healthy arteries of carotid interna type.

III. Thesis [3, 8]

I made a numerical model with finite volume based method which is suitable to simulate the rigid body motion of red blood cells – having slightly smaller diameter than the blood vessel – in capillaries having rigid walls. I examined the cases of one or two red blood cells in the centre line of the tube perpendicularly to the direction of flow. With that numerical model I reproduced the occurrence: of the so called “bolus-flow” phenomenon.

I made a numerical model with finite volume based method which is suitable to simulate the motion of a red blood cell with realistic parameters – having slightly smaller diameter than the blood vessel – in a capillary having elastic material parameters. I eliminated the difficulties caused by mesh deformation by anchoring the frame of reference to the red blood cell.

I proved with numerical simulations that in this special case, when the red blood cells file through the capillary, the increased shear stress arising in the arterial wall near the red blood cells gives the primary extra load in the wall.

IV. Thesis [3, 8]

I verified with discrete element based two dimensional numerical simulation that in arteries greater then capillaries in the case of one red blood cell, the red blood cell turns in the direction of the flow, if that diameter is the half of the diameter of the blood vessel.

With a purely discrete element based method I created a two dimensional numerical model which is suitable to simulate the motion of red blood cells having real material parameters in arterioles surrounded by endothelial cells having real material parameters, but it did not make investigations of fluid dynamics possible. In the case of a bifurcation I determined
with numerical simulations the redundancy stresses at the wall arising from the collisions of red blood cells, if the diameter of red blood cell is half/third of the diameter of the tube and the size of endothelial cells corresponds to the diameter of the tube.

3. SUMMARY AND OUTLOOK

My aim was to determine what numerical methods are suitable for the analysis of the flow of red blood cells in arteries of various diameters, and to determine the stresses in the endothelial cells, which form the inner wall of the vessels, in the range of vessels where the dimension of the red blood cells cannot be neglected with respect to the diameter of the vessel. My conclusions are as follows:

1) The so-called particle transport method (purely continuum based modelling) can be applied for arteries of diameter up to mm approximately, i.e. to 100 multiple of the size of the red blood cells – solid particles carried in the flow.

2) When the extent of the red blood cells in the fluid becomes significant, one needs to switch from the purely continuum based fluid dynamics modelling to the coupled fluid dynamics-discrete element modelling. Arterioles with diameter of 150 μm (anterooms of capillaries) are just within the domain of applicability of this method. The diameter of the vessel can as small as 25 times the size of the red blood cells.

3) Entering the domain of arterioles, one needs to switch to a purely discrete element modelling. Based on discrete element modelling one can go as far as the domain of capillaries.

4) Finally, I investigated the case separately, when the red blood cells move in a single file in the tube formed by the endothelial cells. Again I recommended the continuum base modelling. This case was important to analyse also because in this domain the extra loading on the wall is not generated primarily by the collisions of red blood cells with the wall but by the increased shear stresses due to the changing fluid field around the red blood cells.

The research presented in my dissertation can be extended along the following lines (without attempting to be comprehensive):

1) Incorporating the effects of biochemical processes controlled by the endothelial layer,
2) modelling the effects of blood vessel narrowing, alluvia,
3) considering other cell components of the blood,
4) examining the effects of stents,
5) modelling other diseases, e.g. anaemia, etc.

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MY PUBLICATIONS IN THE TOPIC OF THE DISSERTATION

Conference article


Journal article

8. Tóth, B.K. – Bojtár, I.: Analysis of the mechanical behavior of discrete element in fluids (from the continuum to the discrete), Biomechanica Hungarica, 3 (1) (2010), pp. 256-264

Book chapter


Conference presentation


Seminar lecture

Other (TDK, Degree work)

REFERENCES IN THE BOOKLET