Blood damage measures for ventricular assist device modeling

Dhruv Arora[1], Marek Behr[1] and Matteo Pasquali[2]
[1] *Department of Mechanical Engineering and Materials Science, MS321,*
[2] *Department of Chemical Engineering, MS362,*
Rice University, 6100 Main St., Houston, TX 77005, USA.

Abstract

The development of implantable ventricular assist devices–in particular, continuous-flow axial and centrifugal pumps–offers hope to many heart attack victims waiting for donor hearts. These autonomous devices are intended as a medium-term bridge to transplant, or, if enough progress is made, even as a permanent clinical solution. One challenge that needs to be addressed in the design phase of blood pumps is the elevated level of shear stress, and the hemolysis response of the red blood cells, which depends on both the dose and time of exposure. The distribution of the shear stress levels in a complex flow field of a rotary blood pump chamber, as well as the measure of the blood cells' exposure to these pathological conditions, are difficult to obtain experimentally. Device designers often have to make decisions on the details of pump configuration guided only by the global, time- and space-averaged, indicators of the shear stress inside the pump, such as the hemoglobin release measurements made on the exiting blood stream. In the context of fluid mechanical modeling of the implantable GYRO blood pump being developed at the Baylor College of Medicine, we are devising tensor-based measures of accumulated strain experienced by individual blood cells, and correlating them with available blood damage data. In the first approximation, red blood cells under shear are modeled as deforming droplets, and their deformation is tracked along pathlines of the computed flow field. We propose ways of deriving standard blood damage indicator from the measure of cell deformation and report blood damage results in an unsteady blood flow simulation in a model two-dimensional pump.

1 Introduction

Design of ventricular assist devices (VADs) poses a tremendous challenge due to the complex physical and chemical nature of blood. Most traditional blood handling devices were designed by experimentation, and only recently computational fluid dynamics (CFD) is evolving as an important design tool. Burgeen *et al* [1] reviewed CFD-based holistic design process of rotary blood pumps and pointed to the need of coupling between hematologic and hydraulic design. Unlike the hydraulic design process, the hematologic design is not well formulated. Blood damage (hemolysis) and blood aggregation (thrombosis) are two important features of hematologic design. A clear understanding of both these processes in complex flow situations is yet to be formed.

Blood is a suspension of formed elements (red blood cells, white blood cells and platelets) in a Newtonian liquid (plasma) of viscosity 1 mPa·s. Red blood cells (RBC) form the major and the largest constituent of blood. They behave as neutrally buoyant microcapsules with tremendous deformabilty but small areal stretchability. A RBC at rest is a biconcave disc of a viscoelastic membrane filled with Newtonian liquid (viscosity $\approx$ 6 mPa·s). The RBC membrane has a relaxation time of approximately 200 ms which depends on the age of the cell [2] and it can support an estimated areal strain of 6% before rupture [3]. Owing to its biconcave shape, a RBC has 40% excess surface area compared to a sphere of the same volume. The excess surface enables RBCs to undergo both volume and surface area preserving deformations. Hemolysis starts when the RBC membrane stretches, developing holes, and leaks hemoglobin–free hemoglobin in the blood stream is toxic. Catastrophic hemolysis occurs when the RBC membrane ruptures. CFD-based hematologic design of an efficient VAD needs a realistic model of blood damage. A few scalar-parameter-based hemolysis models have appeared in the literature over the past decade. Bludszuweit [4] proposed an instantaneous scalar stress measure for hemolysis prediction. Yeleswarapu *et al* [5] developed a scalar damage accumulation model which incorporates aging of RBCs. This latter model requires a damage function which remains unknown in complex flow situations. Even though extensive experimental studies have been done to understand steady-state hemolysis there have been been only few unsteady flow studies. Also there is a lack of consensus on a model for steady/unsteady hemolysis. Models based on the accumulation of damage along the pathlines induced by high shear stress and models based on the local instantaneous strain rate are currently used for correlating flow calculations with hemolysis. Here we propose a tensorial strain model for predicting hemolysis based on the RBC deformation. This model is tuned with experimental data on flow-induced RBC deformation. Differences between the tensorial strain model and the scalar stress measure are highlighted in simple shear flow and in a prototypical two-dimensional blood pump.

2 CFD of blood flow

Blood flow is modeled by the momentum and mass conservation equations for an incompressible fluid,

$$\rho\left(\frac{\partial \mathbf{u}}{\partial t}+\mathbf{u}\cdot\nabla\mathbf{u}-\mathbf{f}\right)=\nabla\cdot\sigma, \tag{1}$$

$$\nabla\cdot\mathbf{u}=0, \tag{2}$$

where ρ is blood density, $\mathbf{u}$ is velocity, σ is stress and $\mathbf{f}$ denotes body forces per unit mass (e.g. gravity). The problem is closed by prescribing an appropriate constitutive equation for the stress. Blood is a shear-thinning viscoelastic fluid; Yeleswarapu *et al* [6] showed that a generalized Oldroyd-B constitutive equation can describe well the shear flow behavior of blood. Here for simplicity we treat blood as a Newtonian liquid,

$$\sigma=\mu\left(\nabla\mathbf{u}+\nabla\mathbf{u}^{T}\right), \tag{3}$$

where μ is dynamic viscosity of blood. Thus, eqs(1) and (2) reduce to incompressible Navier-Stokes equations. These equations are solved by the stabilized space-time finite element method. Rotating parts are handled with the shear-slip mesh update method. The velocity and pressure data is further post-processed to obtain the high wall shear stress regions. Reference [7] reports the details of the method and a complete three-dimensional analysis of the GYRO centrifugal blood pump.

3 Hemolysis

Hemolysis is the premature damage of RBCs which otherwise have a normal life span of 120 days for a healthy person. Damage due to shearing (mechanical hemolysis) is the main cause of hemolysis in VADs, and for over four decades steady-shear hemolysis studies have been performed to develop an understanding of this process [3].

Flow rate in a typical VAD matches that of a human heart (5 l/min); the characteristic residence time of a RBC in a VAD is approximately 500 ms. Giersiepen *et al* [8] developed a correlation for steady-shear hemolysis on this time scales based on Wurzinger *et al*'s [9] experiments done in a Couette system. The correlation is:

$$\frac{\Delta Hb}{Hb}=3.62\times10^{-7}\ \tau^{2.416}\ \Delta t^{0.785}, \tag{4}$$

where $\frac{\Delta Hb}{Hb}$ is ratio of plasma free hemoglobin to total hemoglobin in the sample, τ is shear stress (Pa) and Δt is exposure time (s). A plot of percentage hemolysis vs. applied shear stress and exposure time is shown in Fig. 1. Hemolysis predictions based on the above correlation in pulsatile blood pump have been reported recently by Okamoto *et al* [10]. Hereafter, the instantaneous stress along a pathline denoted by τ and such a method is termed "stress-based".

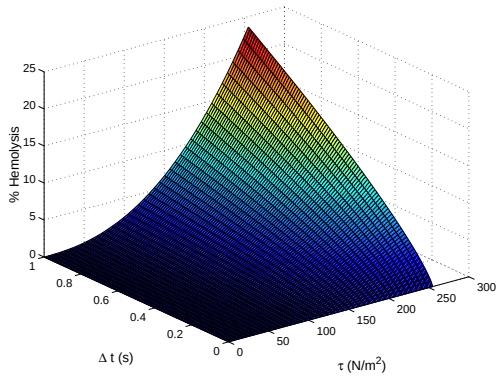


Figure 1: Hemolysis correlation for steady shear flow.

4 Red blood cells in shear flow

The RBCs aggregate into a coin stack shape structure (rouleaux) at rest, which breaks as shear stress increases. As reported by Schimid-Schonbein and Wells [11], the RBCs preserve their biconcave shape and tumble till shear stress of ≈ 0.1 Pa. The tumbling gradually reduces and the cells begin to align with the flow at $\approx$ 0.2 Pa. The RBCs deform into ellipsoidal shape, orient with the flow and show tank-treading at 1 Pa. The tank-treading and deformation into ellipsoidal shape has been confirmed in several later experimental studies. Leverett *et al* [12] found that above 150 Pa, hemolysis occurs primarily in the bulk rather than near walls. This shear stress corresponds to shear rate of 50000 s^{-1} for whole blood. The RBC membrane is believed to reach its 6% areal strain limit at this shear-rate.

5 Tensor based model of red blood cell deformation

We consider a RBC in a general flow as a neutrally buoyant droplet. The velocity gradient $\nabla \mathbf{u} = \mathbf{E} + \mathbf{W}$ can be decomposed into the symmetric strain rate tensor $\mathbf{E}$ and the antisymmetric vorticity tensor $\mathbf{W}$. The shape of the droplet is described by a symmetric, positive definite second rank morphology tensor $\mathbf{S}$. Maffettone *et al* [13] proposed a droplet deformation equation which is modified here to include the tank-treading phenomenon. The frame invariant modified equation is:

$$\mathbf{S}^{\circ} = -\frac{f_1}{\tau}\left[\mathbf{S} - g(\mathbf{S})\mathbf{I}\right] + \ f_2\left[\mathbf{E}\cdot\mathbf{S} + \mathbf{S}\cdot\mathbf{E}\right] + \ f_3\left[\widetilde{\mathbf{W}}\cdot\mathbf{S} - \mathbf{S}\cdot\widetilde{\mathbf{W}}\right], \qquad (5)$$

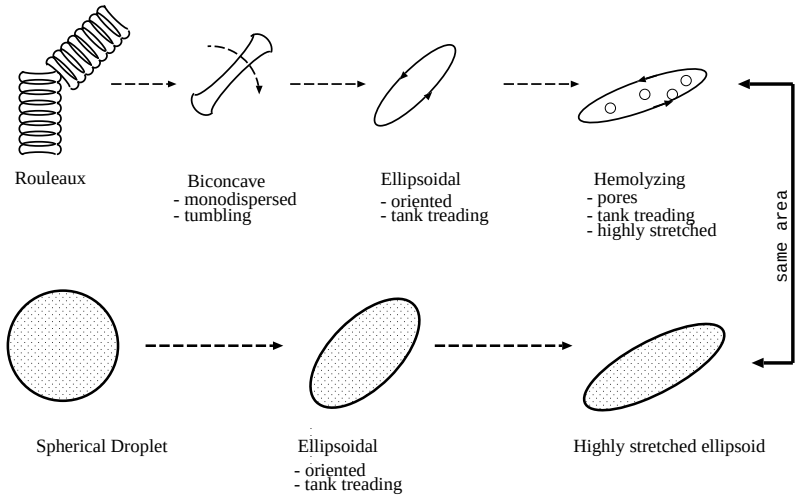


Figure 2: Red Blood cell in shear flow and model

where:

$$\mathbf{S}^{\circ} = \frac{d\mathbf{S}}{dt} - [\Omega \cdot \mathbf{S} - \mathbf{S} \cdot \Omega], \tag{6}$$

$$\widetilde{\mathbf{W}} = \mathbf{W} - \Omega, \tag{7}$$

$$g(\mathbf{S}) = \frac{3\,III}{II}, \tag{8}$$

$$\Omega = \mathbf{e}_i \frac{d\mathbf{e}_i}{dt} = \mathbf{e}_i \left(\frac{\partial \mathbf{e}_i}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{e}_i \right). \tag{9}$$

Ω is rate of rotation of the eigenvectors $\mathbf{e}_i$ of $\mathbf{S}$. II and III are second and third invariants of $\mathbf{S}$, respectively. It is assumed that the shape of the droplet remains ellipsoidal at all times, and the volume of the droplet is preserved. The first term on the right hand side of eq (5) models the shape recovery of the droplet in absence of shear stress. The second term represents the nonaffine deformation of the droplet. The third term captures the tank treading motion which reduces the vorticity seen by the droplet. The reduction in vorticity was shown by Roscoe [14] for the case of tank-treading stationary ellipsoids and applied to RBCs by Keller and Skalak [15]. The eigenvalues of $\mathbf{S}$ are the squared lengths of the three axes of ellipsoid. Fig. 2 shows the red blood cells in shear flow as compared to the proposed model.

6 Parameters

The parameters in eq (5) are chosen to match the steady shear experimental observations reported in the literature. Because the relaxation time of RBCs is approxi-

mately 200 ms we set:

$$\frac{f_1}{\tau} = 5.0 \text{ s}^{-1}. \tag{10}$$

In various experiments it is observed that RBC membrane does not oscillate in the shear flow. But the droplet model shows damped oscillations at changing shear rates when $f_2 \neq f_3$; thus, we restrict $f_2 = f_3$. In a shear flow with

$$\nabla \mathbf{u} = \begin{bmatrix} 0 & G & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & G/2 & 0 \\ G/2 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & G/2 & 0 \\ -G/2 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{11}$$

the steady state droplet deformation equation becomes:

$$\frac{f_1}{\tau} (\mathbf{S} - g(\mathbf{S})\mathbf{I}) = f_2 \left(\nabla \mathbf{u} \cdot \mathbf{S} + \mathbf{S} \cdot \nabla \mathbf{u}^T \right). \tag{12}$$

The eigenvalues of $\mathbf{S}$ in eq(12) are:

$$W^2 = \lambda_1 = \left(\frac{f_1^2}{f_1^2 + \tau^2 f_2^2 G^2} \right)^{1/3}, \tag{13}$$

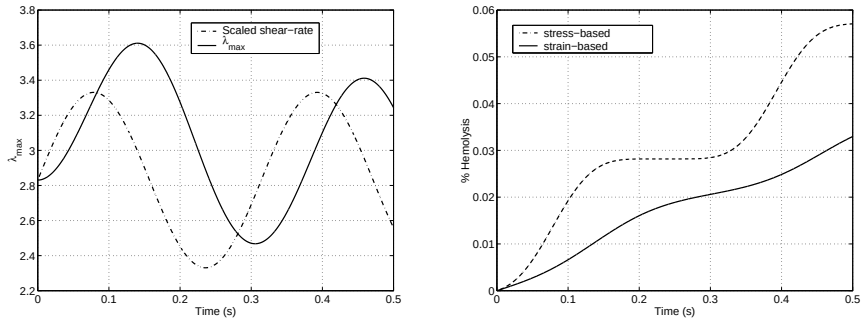
$$L^2 = \lambda_2 = \left(\frac{f_1^2}{f_1^2 + \tau^2 f_2^2 G^2} \right)^{1/3} \left[\frac{(f_1^2 + \tau^2 f_2^2 G^2) + \tau G f_2 \sqrt{f_1^2 + \tau^2 f_2^2 G^2}}{f_1^2} \right], \tag{14}$$

$$B^2 = \lambda_3 = \left(\frac{f_1^2}{f_1^2 + \tau^2 f_2^2 G^2} \right)^{1/3} \left[\frac{(f_1^2 + \tau^2 f_2^2 G^2) - \tau G f_2 \sqrt{f_1^2 + \tau^2 f_2^2 G^2}}{f_1^2} \right], \tag{15}$$

where λ_1, λ_2 and λ_3 are eigenvalues, and L, B and W are three axial lengths of the droplet. As shown in Fig. 2 the droplet configuration is matched with the hemolyzing RBC (6% areal strain at 50000 s^{-1}). The area of general-ellipsoidal droplet is computed by a series used by Keller and Skalak [15] for RBC. A RBC has 40% excess surface area than a droplet of same volume and undergoes 6% areal strain before hemolyzing; therefore, a droplet with same volume as RBC stretches to 1.4×1.06 times its original surface area. Matching the droplet configuration with a hemolyzing RBC gives:

$$f_2 = f_3 = 1.05 \times 10^{-3}. \tag{16}$$

Thus, the 3 parameters f_1/τ, f_2 and f_3 together incorporate relaxation time, lack of membrane oscillations, tank-treading and areal strain limit into the model.



(A) (B)

Figure 3: Sinusoidal shear flow (G_0 = 5000 s^{-1}; ω = 20 s^{-1}): (A) maximum eigenvalue ($f_1 = 5\ s^{-1},\ f_2 = f_3 = 1.05 \times 10^{-3}$); (B) hemolysis.

7 Hemolysis prediction

An instantaneous droplet shape distortion $D = (L-B)/(L+B)$ is computed with axial lengths of the droplet. This instantaneous distortion can be caused by a steady shear rate G_{eff} and corresponding steady shear stress τ_{eff} given as:

$$G_{\text{eff}} = \sqrt{\frac{f_1^2\ D^2}{(1-D^2)\ \tau^2\ f_2^2}}, \tag{17}$$

$$\tau_{\text{eff}} = \nu_{blood}\ G_{\text{eff}}. \tag{18}$$

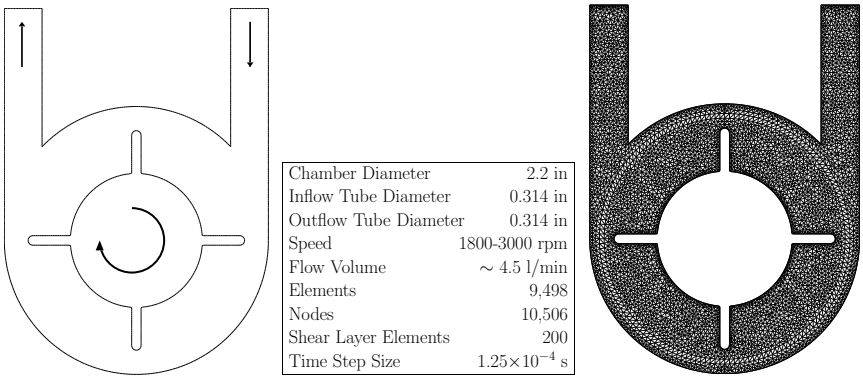
We use this steady shear stress in eq (4) to estimate instantaneous hemolysis. This gives a hemolysis correlation based on the instantaneous distortion D while using the steady-shearing predictions. The hemolysis predictions with this relation are hereafter called "strain-based". In the next section the strain-based hemolysis predictions are compared with the instantaneous stress based (stress-based) hemolysis predictions.

8 Numerical results

Eq (5) is integrated along the pathlines in a flow to obtain RBC deformation which is then used in eq (4) to estimate hemolysis. For a steady shear experiment, the modeled RBC membrane stress τ_{eff} is same as instantaneous shear stress τ and thus both strain-based and stress-based models predict the same levels of hemolysis.

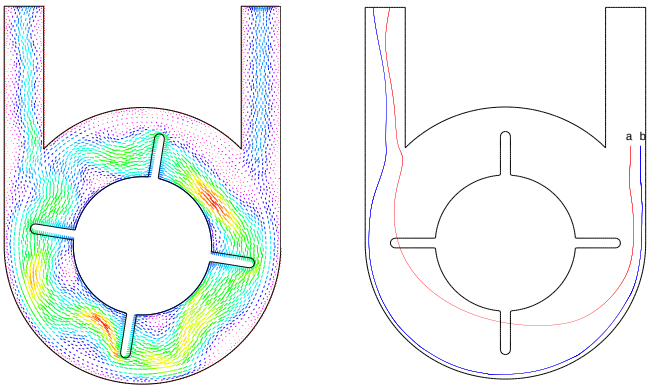
8.1 Sinusoidal shear

The predictions of the strain-based and stress-based models are compared on a homogeneous flow that superimposes steady and sinusoidal shearing, described



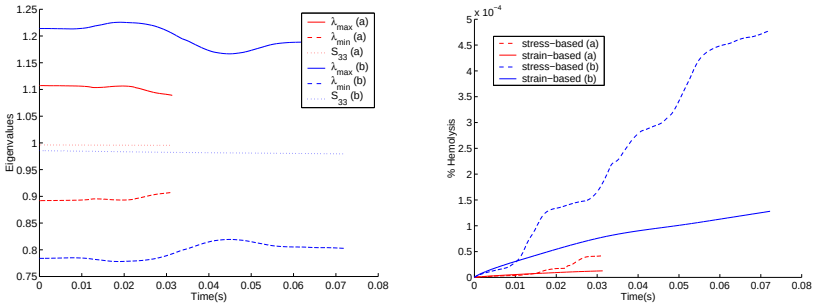
Chamber Diameter	2.2 in
Inflow Tube Diameter	0.314 in
Outflow Tube Diameter	0.314 in
Speed	1800-3000 rpm
Flow Volume	$\sim$ 4.5 l/min
Elements	9,498
Nodes	10,506
Shear Layer Elements	200
Time Step Size	1.25×10^{-4} s

Figure 4: 2-dimensional pump: geometry and mesh.



(A) (B)

Figure 5: 2-dimensional pump : (A) velocity after 7 revolutions; (B) pathlines.



(A) (B)

Figure 6: 2-dimensional pump: (A) eigenvalue of morphology tensor; (B) hemolysis.

by:

$$G(t) \equiv \frac{du_x}{dy} = G_0\,(1+\sin(\omega t))\,. \tag{19}$$

Similar flow is observed in VADs where a baseline shearing is superimposed with a periodic impulse caused by rotating impeller. Fig.3 shows the maximum eigenvalue of **S** in comparison with the sinusoidal impulse. The eigenvalue lags the impulse due to viscoelastic nature of the membrane. It also shows the accumulated hemolysis as predicted by strain-based and stress-based model after starting of sinusoidal shearing.

8.2 Hemolysis in 2-dimensional pump

A simplified version of a three-dimensional centrifugal blood pump (PI710[1]) is constructed to test the hemolysis model. Fig. 4 shows the geometry of the blood pump and a hybrid structured/unstructured mesh. Incompressible flow in the pump is computed with stabilized space-time finite element method and velocity after 7 revolutions is shown in Fig. 5[2]. Two pathlines are traced in the flow and the droplet deformation is computed along the pathlines using Euler integration scheme. Fig. 6 shows the changes in eigenvalues of morphology tensor and the hemolysis prediction along these pathlines. The strain-based model predicts significantly lower hemolysis than the stress-based estimate.

9 Conclusions

In this work, a tensor-based blood damage model is proposed and implemented for CFD simulations of blood flow in two-dimensional blood pump. The model is developed using an analogy between RBC and droplets. It incorporates experimentally-measured quantities–relaxation time, excess surface area and hemolysis threshold strain rate, and experimentally-observed phenomena–tank-treading and ellipsoidal deformation. The model accounts for estimated areal strain limit of the RBC membrane. The model relates the RBC deformation due to instantaneous shearing with the steady shearing hemolysis experiments. The model's strain-based hemolysis predictions are compared with the stress-based predictions in three different flow simulations. While both models predict the same level for hemolysis in steady shearing, a large difference is observed in unsteady shearing flows. Albeit in a simplistic way, the strain-based model accounts for the physical phenomena of RBC membrane stretching and is thus a suitable candidate for realistic hemolysis predictions.
A further calibration and validation of model can be accomplished if a sinusoidal shearing flow experiments are available. The proposed model can be used to optimize the VAD design by minimizing the deviation of the morphology tensor from identity over a family of pathlines.

[1] A centrifugal blood pump under development at Baylor College of Medicine, Houston, TX
[2] An article in color available at www.ruf.rice.edu/∼mp/articles/wit2003a.pdf

References

[1] Burgreen, G.W., Antaki, J.F., Wu, Z. & Holmes, A.J., Computational fluid dynamics as a development tool for rotary blood pump. *Artificial Organs*, **25(5)**, pp. 336–340, 2001.

[2] Hénon, S., Lenormand, G., Richertm, A. & Gallet, F., A new determination of the shear modulus of the human erythrocyte membrane using optical tweezers. *Biophysical Journal*, **76(2)**, pp. 1145–1151, 1999.

[3] Blackshear, P. & Blackshear, G., Mechanical hemolysis. *Handbook of Bioengineering*, eds. R. Skalak & S. Chien, McGraw-Hill: New York, USA, pp. 15.1–15.19, 1987.

[4] Bludszuweit, C., Model for general mechanical blood damage prediction. *Artificial Organs*, **19(7)**, pp. 583–589, 1995.

[5] Yeleswarapu, K., Antaki, J., Kameneva, M. & Rajagopal, K., A mathematical model for shear-induced hemolysis. *Artificial Organs*, **19(7)**, pp. 576–582, 1995.

[6] Yeleswarapu, K., Kameneva, M., Rajagopal, K. & Antaki, J., The flow of blood in tubes: Theory and experiments. *Mechanics Research Communications*, **25(3)**, pp. 257–262, 1998.

[7] Behr, M. & Arora, D., Shear-slip mesh update method: Implementation and applications, 2003. To appear in *Computer Methods in Biomechanics and Biomedical Engineering*.

[8] Giersiepen, M., Wurzinger, L., Opitz, R. & Reul, H., Estimation of shear stress-related blood damage in heart valve prostheses - *in vitro* comparison of 25 aortic valve. *International Journal of Artificial Organs*, **13(5)**, pp. 300–306, 1990.

[9] Wurzinger, L., Opitz, R. & Eckstein, H., Mechanical bloodtrauma. an overview. *Angeiologie*, **38(3)**, pp. 81–97, 1986.

[10] Okamoto, E., Hashimoto, T. & Inoue, T., Blood compatible design of a pulsatile blood pump using computational fluid dynamics and computer-aided design and manufacturing technology. *Artificial Organs*, **27(1)**, pp. 61–67, 2003.

[11] Schmid-Schonbein, H. & Wells, R., Fluid drop-like transition of erythrocytes under shear. *Science*, **165**, pp. 288–291, 1969.

[12] Leverett, L., Hellums, J., Alfrey, C. & Lynch, E., Red blood damage by shear stress. *Biophysical Journal*, **12**, pp. 257–273, 1972.

[13] Maffettone, P. & Minale, M., Equation of change for ellipsoidal drops in viscous flow. *Journal of Non-Newtonian Fluid Mechanics*, **78**, pp. 227–241, 1998.

[14] Roscoe, R., On rheology of a suspension of viscoelastic spheres in a viscous liquid. *Journal of Fluid Mechanics*, **29**, pp. 273–293, 1967.

[15] Keller, S. & Skalak, R., Motion of a tank-treading ellipsoidal particle in shear flow. *Journal of Fluid Mechanics*, **120**, pp. 27–47, 1982.